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The Ethics of Research with Human Subjects

Protecting People, Advancing Science, Promoting Trust

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The Ethics of Research with Human Subjects

Protecting People, Advancing Science, Promoting Trust

Springer

David B. Resnik
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Abbreviations

AAMC	Association of American Medical Colleges
ART	Anti-retroviral therapy
CDC	Centers for Disease Control and Prevention
CHEERS	Children's Environmental Exposure Research Study
CIA	Central Intelligence Agency
CIOMS	Council for International Organizations of Medical Sciences
COI	Conflict of interest
DHHS	Department of Health and Human Services
DMC	Decision-making capacity
DNA	Deoxyribonucleic acid
DSMB	Date and safety monitoring board
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accessibility Act
HIV	Human immunodeficiency virus
HRPP	Human research protection program
IRB	Institutional review board
LAR	Legally authorized representative
NPRM	Notice of proposed rulemaking
NRC	National Research Council
NSF	National Science Foundation
OHRP	Office of Human Research Protections
ORI	Office of Research Integrity
PHS	Public Health Service
QA/QI	Quality assurance/quality improvement
RCT	Randomized controlled trial
REB	Research ethics board
SAE	Serious adverse event
SOPs	Standard operating procedures
SUPPORT	Surfactant, Positive Pressure, and Oxygenation Randomized Trial
UP	Unanticipated problem
WMA	World Medical Association

Chapter 1
Introduction

Research with human subjects[1] exemplifies the perennial conflict between the good of the individual and the good of society. Policies and procedures that protect the rights and welfare of human subjects may hinder scientific research that benefits society. Due to this conflict, research with human subjects continues to be one of the most controversial topics in bioethics, despite ample government regulation, institutional oversight, and professional guidance. Nearly every week, the media brings a new issue, problem, or scandal to the public spotlight, with predictable responses from concerned citizens, compliance officials, and investigators. Concerned citizens and compliance officials often react to new developments by calling for additional regulation and oversight, while investigators frequently object that they are already inundated with red tape and that new rules will impede important scientific research without yielding significant benefits for human subjects or society (Klitzman 2015). The following examples illustrate some of the ethical dilemmas that arise in research involving human subjects.

[1] Some authors use the term 'participant' instead of 'subject' because they regard the term 'subject' as demeaning (Chalmers 1999). Though I will sometimes use the term 'participant' in this book, I will, for the most part, stick with the term 'subject.' My reasons for this word choice are threefold. First, federal regulations and other guidance documents use the term 'subject.' Second, the word 'participant' is somewhat misleading because it implies a degree of active participation and collaboration that is not always present in research. Sometimes people are involved in research passively, e.g. when an investigator analyzes existing biological samples to discover relationships between genetics and disease. Third, 'participant' is a feel-good term that can obscure the very real potential for exploitation or mistreatment that can occur when investigators study people. Using the term 'subject' reminds us that people are being studied.

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1.1 Perinatal HIV Prevention Trials

In the 1990s, many developed nations faced an epidemic of perinatal transmission of the human immunodeficiency virus (HIV), with hundreds of thousands of babies becoming infected from their mothers each year. In response to this public health crisis, the National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC) sponsored 18 randomized, controlled trials (RCTs) involving 17,000 women to determine whether a short course of the drug zidovudine would be effective at preventing this type of infection. Sixteen of the trials were conducted in developing nations, including Burkina Faso, Côte d'Ivoire, the Dominican Republic Ethiopia, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, and Zimbabwe (Lurie and Wolfe 1997). A drug regimen known as the 076 protocol had been proven to be effective at reducing perinatal HIV transmission, but it used about $800 worth of ziduvudine and was difficult to implement, as it required the administration of the drug throughout pregnancy. As a result, the 076 protocol was not affordable or practical for most people in developing countries. The short course was more affordable and practical, because it used $80 worth of ziduvudine administered to the mother before, during, and after labor and delivery, and to the child at birth (Varmus and Satcher 1997). The purpose of the trials was to determine whether the short course would be more effective than the treatment that patients had available to them in the host nations, which was no antiretroviral therapy. The trials were reviewed and approved by institutional review boards (IRBs) and ethics committees at the NIH and CDC, and in the host nations. They also had the support of the Joint United Nations Programme on HIV/AIDS (Varmus and Satcher 1997).[2]

While the trials were underway, two scientists from the consumer interest group Public Citizen, Peter Lurie and Sydney Wolfe, published an article in the *New England Journal of Medicine* in which they argued that 15 of the trials with placebo control groups were unethical[3] because ziduvudine been proven effective at reducing perinatal HIV transmission. They argued that these trials should have used an active control design, i.e. a design comparing different ziduvudine regimens. They also noted that 3 of the trials, including 2 conducted in the US, used an active control design. It was unethical to use placebo control groups, according to Lurie and Wolfe, because this involved withholding an effective treatment from seriously ill mothers and their babies (Lurie and Wolfe 1997). *New England Journal of Medicine* editor Marcia Angell (1997) wrote an editorial supporting Lurie and Wolfe's

[2] In the U.S. committees that oversee research with human subjects are called IRBs. In other countries, they may be called research ethics boards (RECs) or research ethics committees (REBs). The points I make concerning IRBs also apply to RECs and REBs.

[3] Some philosophers hold that 'ethics' refers to the standards of conduct for a particular group or profession, i.e. medical ethics, whereas 'morality' refers to more general standards. I will use the terms 'ethics' and 'morality' more or less interchangeably in this book. I do not find the distinction between 'ethics' and 'morality' to be very useful because laypeople usually do not make this distinction. Insisting on using a philosophical distinction which does not reflect common practice may be confusing to readers not schooled in this particular way of speaking.

critique. Angell compared the trials to the infamous Tuskegee Syphilis study[4] and accused the researchers of subscribing to a double-standard: one for developed nations and a different one for developing nations (Angell 1997).

NIH Director Harold Varmus and CDC Director David Satcher responded to these critiques by arguing that placebo control groups were necessary to determine whether the short course would work better than the prevailing standard of care in the host countries and to ensure that the trials would be scientifically rigorous and could be completed in a timely fashion. They said that committees reviewing the studies had considered the active control design but decided to include placebo groups because an active control design would require a larger sample than a placebo control design because it would involve detecting smaller differences between treatment groups.[5] Thus, RCTs with active control groups would require more research subjects and take longer to complete than those with placebo control groups. They might also yield inconclusive results (Varmus and Satcher 1997).

The controversial HIV prevention studies involve a conflict between the welfare of individuals and the good of society (Resnik 1998). The active control design provides more benefits to subjects in the study than the placebo control design but may provide fewer benefits to society as a whole because it may take longer to conduct. The placebo design denies benefits to subjects in the control groups but may benefit more people overall because it will take less time to conduct (Varmus and Satcher 1997). As it turned out, the trials proved that a short course of zidovudine is more effective than a placebo in reducing perinatal HIV transmission (Dabis et al. 1999).

While the HIV prevention trials did not lead to new government regulations, they did increase awareness among researchers and bioethicists about the ethical issues in conducting research in developing nations (Wendler et al. 2004). The World Medical Association (WMA) also decided to revise its Declaration of Helsinki to clarify its stance on the use of placebos in medical research (Lie et al. 2004). The latest revision of the WMA guidelines states that placebos may be used when:

> [N]o proven intervention exists, the use of placebo, or no intervention, is acceptable; or [w]here for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option (World Medical Association 2013).

The 2013 revision of the Helsinki Declaration would not have permitted the controversial HIV prevention trials because subjects receiving a placebo might experience serious or irreversible harm. Other international groups have rejected the WMA's restrictive stance on the use of placebos in medical research, and the Food and Drug

[4] See discussion of this study in Chap. 2.

[5] The sample size likely to yield statistically significant results from a study is inversely proportional to the size of the effect one is attempting to detect: the smaller the effect, the larger the sample size (Blair and Taylor 2007).

Administration (FDA) no longer requires that international research submitted to the agency follow the Helsinki Declaration (Lie et al. 2004).

1.2 The SUPPORT Study

For a more recent example of the conflict between the rights and welfare of individuals and the common good, consider an NIH-sponsored study titled "Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)". The aims of the study were to: (1) understand more about the benefits and risks of using continuous airway pressure (CAP) in helping the lungs of neonates in the intensive care unit (ICU) remain inflated; and (2) to determine the optimal level of blood oxygen saturation for neonates receiving CAP (SUPPORT Study Group 2010). Investigators at 22 institutions enrolled 1316 infants born between 24 and 28 weeks gestation in the study. The University of Alabama at Birmingham (UAB) was the lead institution for the study's second aim. IRBs at each site approved the study (Resnik 2013). The neonates were randomly assigned to receive blood oxygenation maintained at a range of 85–89% or 91–95%. The standard of care (i.e. accepted medical practice) at that time was to maintain oxygenation at 85–95%, so the range in the study fell within the standard of care. Previous studies had shown that higher levels of oxygenation are associated with an increased risk of retinopathy of prematurity (ROP) and that lower levels are associated with an increased risk of brain damage or death (Resnik 2013). The consent document used in the study informed the parents of the risks of monitoring blood oxygenation levels but it did not inform the parents of the risks of random assignment to different treatment groups (Resnik 2013).

On March 7, 2013, the Office of Human Research Protections (OHRP), which oversees Department of Health and Human Services (DHHS)-funded research, sent a determination letter to UAB alleging non-compliance with DHHS regulations, otherwise known as the Common Rule (Office of Human Research Protections 2013).[6] The Common Rule, which has been adopted by 17 federal agencies, requires that research subjects or their representatives be informed about reasonably foreseeable risks (Department of Health and Human Services 2009 at 45 CFR 46.116 a2).[7] OHRP claimed that the study violated this requirement because the consent document did not inform the parents about the risks of randomization. According to OHRP, neonates assigned to the higher oxygenation group faced an increased risk of ROP, while those in the lower oxygenation group faced an increased risk of brain damage or death (Office of Human Research Protections 2013). Public Citizen

[6] NIH is an agency within DHHS.

[7] Unless noted otherwise, references to the Common Rule used in this book will be to the 2009 version. The Obama Administration announced revisions to the Common Rule on January 19, 2017 (Department of Homeland Security et al. 2017), but as of the writing of this book, the Trump administration could still propose its own changes to the regulations or delay their implementation. I will discuss the federal regulations in more depth in Chap. 2.

learned about OHRP's determination letter and asked the DHHS to apologize to the parents of the neonates and conduct an independent investigation of the ethics of the study (Resnik 2013).

Numerous scientists and bioethicists, including SUPPORT investigators and NIH Director Francis Collins and Deputy Director for Science, Outreach and Policy, Kathy Hudson, published commentaries in the *New England Journal of Medicine* and other journals defending the study (Carlo et al. 2013; Drazen et al. 2013; Hudson et al. 2013; Magnus and Caplan 2013; Wilfond et al. 2013). SUPPORT defenders argued that the parents did not need to be informed about the risks of randomization because these risks were not reasonably foreseeable because they were speculative and not based on empirical data (Resnik 2013). Indeed, one of the goals of the study was to determine the risks of blood oxygenation at different ranges (Hudson et al. 2013). Since all neonates were maintained at an oxygen range within the standard of care, the study did not expose them to risks that they would have otherwise been exposed to. SUPPORT defenders also criticized OHRP for its response to the study, arguing that the agency was inappropriately interfering with important research (Drazen et al. 2013; Magnus and Caplan 2013).

SUPPORT critics wrote commentaries and letters defending OHRP's actions (Macklin et al. 2013). Critics argued that the risks of the study had not been appropriately disclosed because the research-related risks were different from the risks of the standard of care, which allows physicians to individualize treatment based on the patient's medical condition. ICU neonates not participating in the study might be maintained at blood oxygen levels determined to be best for them by their physician. For example, a physician might determine that 90% oxygen is the best level for his or her patient. Neonates in study, however, would be maintained at blood oxygen levels in the two treatment groups, as determined by the study protocol not by their individual medical needs (Macklin and Shepherd 2013; Resnik 2013). The risks of randomization might be speculative, but they were still possible and should have been disclosed to the parents (Macklin and Shepherd 2013).

Although commentators on the SUPPORT study framed the issues in terms of the risks of randomization and the obligation to disclose those risks, the controversy also involved, at a deeper level, a conflict between the rights and welfare of research subjects and the advancement of scientific knowledge. It is conceivable that many parents would not have agreed to enroll their children in this study if they had been told about the risks of the randomization. They might have decided that it would be better for their children to receive individualized treatment provided by a physician instead of treatment based on the study's design. Disclosing the risks of randomization would have provided parents with some information pertinent to their decision to enroll their children in the study but it could have hampered the research by making it more difficult to recruit patients.

One of the key features of a clinical trial is that physicians have very little leeway when it comes to deviating from the study protocol. Physicians treating patients in a clinical trial are supposed to follow rules described by the protocol instead of individualizing treatment. They can deviate from the protocol only to protect the health of the patient, and when they do this, they must inform the IRB. Following

the dictates of the study protocol is an important part of rigorous research design, since this helps to control the conditions of the experiment (Miller and Brody 2002). If physicians conducting a clinical trial individualized their treatment, it might be impossible to interpret the results of the study, due to uncontrolled variability related to study interventions and procedures. Patients in a clinical trial need to understand how their treatment may differ from what they would receive outside of the study (Macklin and Shepherd 2013).

The controversy concerning the SUPPORT study did not lead to new research regulations, but it did increase awareness among investigators and bioethicists about the ethical issues involved in clinical trials that attempt to understand differences between treatment modalities within the standard of care, also known as comparative effectiveness research. Additionally, OHRP held a public meeting on issues related to the study and released some guidance on disclosing reasonably foreseeable risks when conducting research that evaluates different treatments falling within the standard of care. According to the guidance:

> [I]f a research study examining standards of care includes as a purpose evaluating identified risks associated with those standards of care, the identified risks associated with the standards of care being evaluated that are different from the risks of standards of care at least some of the subjects would be exposed to outside of the research study are generally considered by OHRP to be reasonably foreseeable risks of research. Reasonably foreseeable risks must be described to prospective subjects when seeking their informed consent (Office of Human Research Protections 2014).

1.3 Hospital Quality Improvement Research

OHRP oversight also generated some controversy in 2007, when the agency investigated a hospital quality improvement research project coordinated by researchers at Johns Hopkins University (JHU) and funded by the Agency for Healthcare Research and Quality (Miller and Emanuel 2008). The project, which began in October 2003, sought to determine whether following an infection control protocol and using a checklist can reduce intravenous (IV) catheter infectious in the intensive care unit (ICU). The protocol included handwashing, cleaning the catheter site with chlorhexidine before insertion, removal of unnecessary catheters, and other procedures (Pronovost et al. 2006). The study was a prospective cohort design, meaning that all participating institutions would follow the protocol and checklist, with data collection before implementation and at 3-month intervals up to 18 months after implementation. One hundred and three ICUs from 67 hospitals in Michigan provided data for the study. Data collection took place from March 2004 to September 2005. The study found that the following the protocol and checklist reduced IV catheter infections significantly: the infection rate fell from 7.7 per 1000 patient days at baseline to 1.4 after 16–18 months (Pronovost et al. 2006).

OHRP began investigating the study when the investigators published their results. The JHU IRB had decided that informed consent from the patients was not

necessary because the study was exempt from IRB review. In its July 19, 2007 determination letter, OHRP stated that the project was not exempt from IRB review and that JHU had failed to comply with DHHS regulations concerning informed consent (Miller and Emanuel 2008). After receiving this letter, the JHU IRB suspended the project.

While there is little question that the project required IRB review because it did not fit one of the categories for exempt research,[8] the need for informed consent from the patients is debatable (Miller and Emanuel 2008). Hospitals routinely implement quality improvement projects designed to protect health and safety without patient consent. As Miller and Emanuel (2008) note, the hospitals in the JHU study could have implemented the infection control protocol and checklist without participating in the study or obtaining patient consent. Miller and Emanuel (2008) argue that the IRB could have waived consent for the study because the federal regulations allow IRBs to waive consent for studies when: "(1) The research involves no more than minimal risk to the subjects; (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) The research could not practicably be carried out without the waiver or alteration; and (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation (Department of Health and Human Services 2009 at 45 CFR 46.116d)." According to Miller and Emanuel (2008), an IRB could have approved a waiver of consent because the study posed minimal risks to subjects; the research could not have been conducted without a consent waiver because it would have been nearly impossible to obtain consent from all ICU patients or their representatives; and waiving consent would not have adversely affected the rights or welfare of the patients.

Since requiring consent for this quality improvement research would probably have prevented it from occurring, the JHU/OHRP controversy also illustrates the dilemma between protecting the rights and welfare of human subjects and promoting scientific research. Although this controversy did not lead to any immediate changes in research regulations, it raised awareness about ethical and oversight issues in hospital quality improvement research (Kass et al. 2013).[9]

1.4 Henrietta Lacks

A biomedical research tool known as HeLa, the first human cell line successfully grown in culture, has been used by millions of scientists and students across the world. Journalist Rebecca Skloot (2010) became curious about this anonymous cell line and wanted learn whom it came from. She discovered that Henrietta Lacks, an African American woman who underwent treatment for cervical cancer at Johns

[8] See Chaps. 2 and 11 for discussion of exempt research.

[9] Earlier versions of the revisions to the Common Rule excluded hospital quality improvement projects from federal research oversight but not the final versions. See Chap. 11.

Hopkins Hospital in 1951, provided the cell line. Skloot interviewed Lacks' family and found out that the tissues used to produce the cell line were extracted from Lacks' tumor without her consent, which was—and still is—a common practice. For many decades, biomedical scientists have been using biological samples left-over from surgical procedures or clinical tests for research projects. Though consent must be obtained to enroll someone in a research study involving the collection of biological samples, it need not be obtained to use de-identified[10] biological samples which are leftover from medical procedures or tests. Skloot also learned that Lacks' family received no financial compensation for the tissues. Skloot's book became a popular best-seller, which was later made into a film. Skloot decided to share profits from her book with the family (Skloot 2010). In 2013, the NIH reached an agreement with Lacks' family concerning access to genomic data from the cell line. The agreement gives the family control over access to the data and recognition on scientific papers (National Institutes of Health 2013).

The Lacks case focused national attention on the issue of informed consent for the use of biological samples in research. A 2015 version of proposed revisions to the Common Rule defined human biological specimens as research subjects, which would have mandated consent for most research involving human biological samples (Department of Homeland Security et al. 2015). While this provision would have enhanced respect for individual autonomy, it was dropped in response to concerns that it would interfere with important biomedical research.[11]

1.5 The Facebook Study

Informed consent was also a major concern in a social psychology experiment conducted using the social network Facebook during January 2012. The investigators manipulated the newsfeeds of 689,003 randomly selected Facebook users to determine whether emotional states can be transferred by social interactions in the absence of verbal cues. They were able to show that users who receive positive feeds are more likely to post positive feeds, while those who receive negative feeds are more likely to post negative ones. The effect was small but significant (Kramer et al. 2014). The authors of the study said that Facebook's user agreement constituted informed consent for the research. All Facebook users must sign a user agreement to participate in this social media forum. The agreement gives the company permission to collect data about the user and conduct research (Facebook 2017). The research generated headlines—and controversy— when it was published in 2014. The journal published an editorial expressing concern about the study's informed consent process, which was below the standards set by the Common Rule. However, the editorial noted that Facebook, as a private company, was not obligated to follow the Common Rule (Verma 2014). While the lead author, Alan Kramer, was

[10] 'De-identified' means that personal identifiers, such as name and address, have been removed.

[11] See the discussion in Chap. 11 of revisions to the Common Rule.

a Facebook employee, the two other authors, James Guillory and Jeffrey Hancock, were associated with Cornell University, which follows the Common Rule. However, Cornell's IRB determined that the federal regulations did not apply to the study, because Guillory and Hancock were not engaged in research with human subjects as they had no interactions with the participants or their private information (Klitzman and Applebaum 2014). While some defended the study because it provided useful information with virtually no risk to the participants, others said the study was unethical because consent via the user agreement did not provide Facebook users with enough information concerning their potential participation in research (Goel 2014; Klitzman and Applebaum 2014).

The Facebook case is an example of significant gap in the U.S. federal research regulations. The human research regulations apply to research funded by federal agencies that follow the Common Rule, or research submitted to the Food and Drug Administration (FDA) or Environmental Protection Agency (EPA) in support of product approvals. Additionally, most institutions that receive federal funding have agreed to apply the Common Rule to all human subjects research they oversee, even research that is not specifically covered by federal regulations (Shamoo and Resnik 2015). Some have argued that the U.S. should close this gap in the federal regulations to ensure uniform protections for all human subjects (Annas 1999; Shamoo and Schwartz 2008). Others, however, have pointed out extending the scope of the federal regulations could impose significant burdens on private companies who are engaged in low-risk research, such as public opinion surveys and marketing studies (Resnik 2008b).

1.6 Overview of This Book

In these examples, conscientious and well-informed scientists and bioethicists reached different conclusions concerning ethical and regulatory issues involving research with human subjects. The researchers, as far as we know, were acting thoughtfully and responsibly and were not egregiously violating laws or ethical standards. They were trying to do what they considered to be ethical research to obtain important results for science and society. Moreover, with exception of the Lacks case, an extensive system of regulating and managing human research with human subjects was already in place when these controversies erupted.

The disagreements occurred at several levels. At one level, the disagreements were about whether a particular study was or was not ethical, or would be ethical if it were modified in a particular way. At another level, the disagreements revolved around the interpretations of regulations and guidelines and their applicability to specific studies. At a third level, the disputes were also about the kinds of policies and oversight systems that should be in place to protect human research subjects. The overarching issue—individual rights/welfare vs. the common good—impacted these disagreements explicitly or implicitly. Scientists and bioethicists came down on different sides of the issue, with some emphasizing protection of research sub-

jects and others emphasizing the promotion of research. Looming in the background were questions about how decisions made by investigators, IRBs, institutions, or oversight officials would impact the public's trust in the research enterprise.

Questions concerning how to adjudicate moral conflicts in research with human subjects will take center-stage in this book. In most of the ethical controversies related to research with human subjects, both sides agree that it is important to protect individual rights/welfare and promote scientific research. The disagreements usually have to do with emphasis or priority-setting. The aim of this book is to develop a philosophical framework for thinking about the ethics of research with human subjects that can be applied to ethical and policy dilemmas like those discussed above.[12] The central insight of this framework is that the goal of promoting trust should play an essential role in our thinking about the ethics of research with human subjects.

Many writers (e.g. Veatch 1987; Levine 1988; Shamoo and Khin-Maung-Gyi 2002; Mazur 2007; Amdur and Bankert 2011; Klitzman 2015) have written books about the ethics of research involving human subjects but very few have attempted to develop a philosophical framework for resolving moral conflicts or guiding policy development. Most of these books provide practical guidance without examining the philosophical issues in-depth. David Wendler (2010) has developed a philosophical framework for thinking about the ethics of pediatric research, but his view has limited applicability because it does not address research involving adults.

Some may object at the outset that there is no need to develop a philosophical framework for thinking about the ethics of research with human subjects because one already exists, namely, the three ethical principles—respect for persons, beneficence, and justice—articulated in the *Belmont Report* (National Commission 1979). While I think that the *Belmont* principles provide useful guidance for the conduct of research with human subjects, I will argue in Chap. 2 that they are not able to adequately address difficult ethical dilemmas because they do not include a method for prioritizing the principles when they conflict, and most controversial issues involve such conflicts. Likewise, the seven ethical principles articulated in a widely cited article by Emanuel et al. (2000) provide useful guidance for research with human subjects but also fall short of the mark because they do include a way of adjudicating conflicts among principles.

Finally, some philosophers, such as Alan Wertheimer (2011), are skeptical of the entire project of developing a philosophical framework for thinking about the ethics of research with human subjects. According to Wertheimer:

> Research ethics is a practical discipline that has developed in response to specific historical events. It is not built on any general or overarching theory. The reining principles…respond to the desire to square the genuine need for biomedical research with the protection of human subjects in the context of a history that contains several episodes of serious abuse and exploitation of human subjects (Wertheimer 2011, p. 3).

[12] By 'policy,' I mean a rule adopted by a government, institution, or organization, such as a statute, regulation, guideline, or code.

While I agree with Wertheimer that the current oversight system largely reflects ad hoc responses to historical events, I think that one can develop a philosophical framework that helps us to understand and critique the current system. While the framework need not be an "overarching theory," it should provide us with some guidance concerning ethical and policy dilemmas.

My plan for the books is as follows. In Chap. 2, I will describe the historical events that Wertheimer refers to and argue that the social and political response to these events has been to develop an oversight system to restore and maintain public trust in research. An important question that emerges from this chapter is whether the current system provides too much or too little protection for human research subjects. To answer this question, we require a philosophical framework for thinking about the ethical dilemmas in research with human subjects.

In Chap. 3, I will consider whether moral theories can provide us with the guidance we are seeking. I will argue that since no single theory satisfactorily accounts for our moral intuitions and addresses crucial objections, some form of moral pluralism is the most reasonable approach. The type of pluralism I adopt, Beauchamp and Childress' (2012) four principles approach, will be familiar to many readers. Since pluralism still leaves us with questions concerning priority-setting when basic principles or values conflict in research with human subjects,[13] we require some additional guidance for dealing with ethical and policy dilemmas.

In Chap. 4, I will develop my trust-based approach more fully. The key premise of the framework is that research is founded on trust: trust between participants and investigators and institutions; between communities and investigators and institutions; among investigators; and between the public and the research enterprise. I will argue that the goal of promoting trust augments other moral principles, and that reflecting on the nature and importance of trust can often help us to decide how resolve ethical and policy dilemmas in research with human subjects.

In Chaps. 5, 6, 7, 8, 9 and 10, I will apply the trust framework to ethical issues in research with human subjects, including informed consent, privacy and confidentiality, risks and benefits in research, vulnerable subjects, and research integrity. In Chap. 11, I will discuss various reforms proposals concerning the current oversight system. In Chap. 12, I will summarize the book's main arguments and conclusions.

Before proceeding further, two comments are in order. First, policy discussions in the book will focus, for the most part, on U.S. regulations and oversight mechanisms, and, to a lesser extent, on international guidelines. Although some may regard the U.S.-focus as narrow-minded, the ethical and legal standards for research with human subjects in the U.S. are similar to those found in other countries (Office of Human Research Protections 2012). Moreover, the U.S. and other

[13] A moral principle is a general rule for conduct, e.g. "do not lie" or "keep your promises." A moral value is something that is morally good or worthwhile. Things have value for their own sake and not as a means to something else are intrinsically valuable. For example, most people would view happiness as intrinsically valuable. Things that have value as a means to something else are extrinsically valuable. For example, most people would regard money as valuable not in itself but for what we buy with it. Some things, such as knowledge and health, may be intrinsically and extrinsically valuable (Timmons 2002).

countries are dealing with similar issues, and the standards adopted in the U.S. have considerable international influence (Brody 1998a). Second, although I will discuss legal and regulatory issues in this book, nothing I say should be taken as legal advice. I am presenting my views to provide investigators and ethicists with some additional tools and perspectives for thinking about research with human subjects. Readers who are interested in legal advice should consult an attorney.

Chapter 2
Historical Background

To understand the ethics of research with human subjects it is important to have some familiarity with important events and trends that have entered the public's consciousness. (See Table 2.1 for a summary of important events.) Examining this historical background will help to frame the issues and provide us with the social, political, economic, and legal context for the current oversight system. The main thesis of this chapter is that the current system has emerged in response to unethical—and in some cases horrific—treatment of human research subjects. According to Alexander Morgan Capron (1989, p. 127), "the darkest moments in the medical annals have involved abuses of human research subjects." Existing guidelines, regulations, principles, and policies are understandably protectionistic because they seek to prevent the kinds of abuses that have generated moral outrage and undermined the public's trust in the research enterprise.

Before describing this historical background, I would like to counteract an impression the reader may draw from the narrative. It may appear to the reader that I think that research with human subjects is always ethically problematic and often morally corrupt. Nothing could be further from the truth. It is my opinion, based on my review of the literature and my experiences as an IRB chair, researcher, and research subject, that most research with human subjects is ethically sound and socially valuable. Research with human subjects has led to the development of medications, vaccines, surgical procedures, medical devices, and psychotherapies which have saved millions of human lives, alleviated suffering, and improved the quality of life. Research has also provided us with important knowledge concerning human biology, psychology, sociology, and anthropology which has helped us gain a better understanding of ourselves and has led applications in medicine, nursing, public health, and other practical disciplines. Research has also provided us with knowledge that has informed public policies (Porter 1999).

It seems that we do not hear enough about the good things that happen in research with human subjects and that we hear too much about the bad. Journalists and ethicists tend to be more interested in bringing scandals and controversies to the public's

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Table 2.1 Human research ethics timeline

400 BCE	Hippocratic oath
1796	Edward Jenner performs a test of a small pox inoculation on eight-year-old James Phipps
1874	Robert Bartholomew inserts electrodes into a two-inch hole in the skull of Mary Rafferty, a mentally disabled cancer patient, and stimulates her brain with electricity
1885	Louis Pasteur administers an experimental rabies vaccine to nine-year-old Joseph Meister without first testing it on animals
1900–1901	Walter Reed's yellow fever experiments
1900	Prussia adopt human research regulations
1932–1972	Tuskegee syphilis study (sponsored by the DHEW)
1932–1945	Japanese experiments on prisoners
1940–1945	Nazi experiments on concentration camp prisoners
1945–1971	The U.S. government sponsors secret human radiation experiments
1946	The AMA adopts ethical guidelines for research with human subjects
1946–1948	The PHS sponsors syphilis prevention experiments in Guatemala
1947	Nuremberg Code adopted
1951	Researchers at Johns Hopkins Hospital develop a cell line from Henrietta Lacks' left over cervical cancer tissue without her consent, which was common practice at the time
1953–1973	The CIA conducts secret mind control experiments
1953–1955	Polio vaccine field trials led by Jonas Salk
1956–1980	Willowbrook hepatitis experiments
1961–1962	Stanley Milgram's obedience to authority experiments
1963	Jewish Chronic Disease Hospital experiments
1964	Helsinki Declaration adopted (first version)
1966	Henry Beecher publishes an exposé on 22 unethical human studies in the *New England Journal of Medicine*
1966	NIH adopts human research regulations
1971	FDA adopts human research regulations
1972	The Associated Press breaks reports on the Tuskegee study
1972	Congressional hearings on biomedical research
1973	Congress passes the National Research Act
1979	The U.S. National Commission releases the *Belmont Report*
1981	U.S. federal agencies implement a major revision of human research regulations
1990	The California Supreme Court rules that physician David Golde and the University of California at Los Angeles were liable for failing to obtain John Moore's informed consent for research they were conducting on his leftover tissue from a splenectomy
1991	Federal agencies revise and unify their research regulations (known as the Common Rule)
1993	Roger Poisson admits to altering patients records in the NSABP clinical trial
1994	President Clinton declassifies thousands of documents pertaining to secret human radiation experiments and creates an advisory committee to examine scientific, ethical, and legal issues related to this research.

(continued)

Table 2.1 (continued)

400 BCE	Hippocratic oath
1997	The U.S. government issues an official apology to participants in the Tuskegee syphilis study and their families
1997	Peter Lurie and Sydney Wolfe publish a paper in the *New England Journal of Medicine* alleging that HIV prevention trials conducted in developing nations were unethical
1998	The U.S. Government Accounting Office issues a report calling for reform of IRBs
1998	Andrew Wakefield publishes a paper in *The Lancet* claiming that the MMR vaccine can cause autism; the journal retracted the paper in 2010 due to ethics problems
1999	Jesse Gelsinger dies in a Phase I human gene therapy experiment; OHRP and the FDA investigate the University of Pennsylvania, where the study occurred
1999	OHRP temporarily halts all human studies at the Duke University Medical Center
2001	Ellen Roche dies in asthma experiment at Johns Hopkins University; OHRP temporarily halts federally-funded research at the university.
2004	The EPA cancels the Children's Environment Exposure Research Study in response to Congressional criticism
2004	Merck withdraws its drug Vioxx from the market, due to safety and liability concerns, including allegations of fraud
2005	Eric Poehlman admits to fabricating and falsifying data on 15 federal grant applications worth $2.9 million; Poehlman serves a year and a day in federal prison as part of a comprehensive legal settlement
2005	Woo Suk Hwang admits to fabricating and falsifying data pertaining to two papers on the derivation of human embryonic stem cells by therapeutic cloning
2006	The EPA revises its human research regulations
2007	OHRP issues a determination letter to Johns Hopkins University claiming that its IRB failed to adequately review a quality assurance research project conducted at 67 hospitals in Michigan
2010	Arizona State University settles a lawsuit with the Havasupai Native American tribe pertaining to improper use of blood samples by researchers
2011	OHRP and the FDA publish an Advance Notice of Propose Rulemaking for revisions to the Common Rule
2013	OHRP issues a determination to the University of Alabama at Birmingham claiming the consent for the SUPPORT study was out of compliance with federal regulations
2015	Federal agencies publish a Notice of Propose Rulemaking for revisions to the Common Rule
2017	Federal agencies publish revisions to the Common Rule

Based in part on Resnik (2012a)

attention than in reporting on the daily interactions between investigators and research subjects where nothing goes wrong and much goes right. Although the historical narrative concerning the ethics of research with human subjects includes many troubling episodes, it is important to come to terms with this storyline and understand its implications for practice and policy.

2.1 Research with Human Subjects Before World War II

I shall begin my review of the history in ancient Greece. Hippocrates (460–377 BCE) is widely recognized as the father of scientific medicine, due to his careful attention to observation and his commitment to explaining diseases as resulting from natural, rather than supernatural, causes (Porter 1999). Hippocrates believed that diseases result from imbalances of different substances (such as blood, phlegm, and mucous) in the body, and most of the Hippocratic interventions were aimed at restoring the body's natural balance and helping the body heal itself. Hippocrates took detailed case histories, observed signs and symptoms in his patients, and kept records on the effectiveness of different cures. Hippocrates also developed a medical ethos known as the Hippocratic Oath. One of the key tenets of the Oath is: "I will use those dietary regimens which will benefit my patients according to my greatest ability and judgement, and I will do no harm or injustice to them (National Library of Medicine 2012)." Others have simplified this part of the Oath to the principle of non-maleficence ("do no harm") and the principle of beneficence ("benefit your patient") (Beauchamp and Childress 2012). Hippocratic medicine therefore tended to be very nonaggressive and observational rather than experimental. Common remedies prescribed by Hippocratic physicians included special diets, herbal medicines, exercise, baths, and massage. The Hippocratic Oath still plays an important role in medical practice, and many medical students take the Oath when they begin their studies (Porter 1999) (Fig. 2.1).

The Hippocratic tradition dominated scientific medicine for 2000 years but yielded to experimentally-oriented approaches during the Scientific Revolution (circa 1500–1700). For example, Paracelsus (1493–1542), Andreas Vesalius (1514–1564), and William Harvey (1578–1657) sought to apply the experimental method to medicine. They dissected animal and human bodies, which allowed them to develop a better understanding of human anatomy and physiology. Although Harvey performed vivisections on animals (to demonstrate, for example, that the heart pumps blood), his experiments on humans tended to be low-risk. Harvey measured pulse and blood pressure and applied tourniquets to human research subjects to demonstrate the direction of blood flow. (Porter 1999).

By the eighteenth century, human experimentation became more common and more risky. For example, on May 14, 1796, Edward Jenner (1749–1823) inoculated James Phipps, an eight-year-old boy, with fluid from a cowpox pustule to determine whether this would prevent him from developing smallpox. Jenner had observed that dairymaids exposed to cowpox seemed to have resistance to smallpox, and

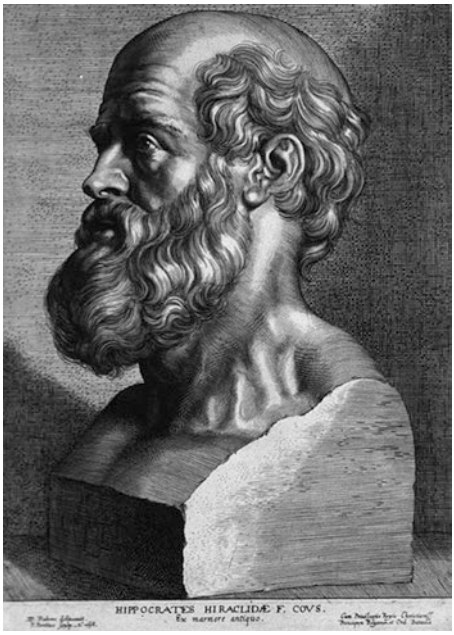

Fig. 2.1 Hippocrates, engraving by Peter Paul Reubens, public domain. https://commons.wikimedia.org/wiki/File:Hippocrates_rubens.jpg

hypothesized that exposure to cowpox would provide protection against smallpox. Phipps suffered no adverse effects from the inoculation other than a slight fever. Six weeks after the inoculation, Jenner exposed Phipps to smallpox, and he did not develop the disease. Jenner also tested this procedure on his children, who also did not contract smallpox (Porter 1999). Louis Pasteur (1822–1896), who developed the germ theory of disease, also tested experimental vaccines on human subjects (Porter 1999). In 1885, Pasteur gave an experimental rabies vaccine to a nine-year old boy, Joseph Meister, without first testing the vaccine on animals. Meister had been mauled by a dog, and Pasteur gave the boy the vaccine in the hope of preventing the disease. The vaccine worked, and other parents asked Pasteur to administer it to their children (Geison 1978). After observing that carbolic acid could reduce wound infections in cattle, Joseph Lister (1827–1912) hypothesized that this compound had antiseptic properties, and he tested it on human subjects. One of the first patients to receive this treatment was James Greenless, an eleven-year-old boy who had a compound fracture of the leg. The boy recovered from his treatment without infection or amputation (Porter 1999) (Fig. 2.2).

Other experiments placed subjects at greater risk and caused more suffering. For example, in 1874 Robert Bartholomew (1831–1904) noticed that his 30-year-old mentally disabled patient, Mary Rafferty, had a two-inch hole in her skull caused by a cancerous ulcer. He took advantage of this opportunity to study her brain and inserted electrodes into the hole. Bartholomew stimulated her brain with electricity and recorded her responses. He noticed that small amounts of electric current caused different bodily movements, depending on the site of the stimulation, but that larger

Fig. 2.2 Louis Pasteur, photo by Félix Nadar Crisco. Licensed under Public Domain via Commons – https://commons.wikimedia.org/wiki/File:Louis_Pasteur,_foto_av_F%C3%A9lix_Nadar_Crisco_edit.jpg#/media/File:Louis_Pasteur,_foto_av_F%C3%A9lix_Nadar_Crisco_edit.jpg

amounts caused pain. The patient fell into a coma and died in a few days, after experiencing distress, convulsions, and seizures (Lederer 1995). In 1897, Giuseppe Sanarelli (1864–1940) claimed to have isolated the bacterium which causes yellow fever from the blood of patients with the disease. To test his hypothesis, he injected the bacteria into five patients without their consent. The patients all developed yellow fever symptoms and three died. William Osler (1849–1919) and many other physicians sharply criticized Sanarelli's experiments (Lederer 1995).

An important medical experiment that helped to pioneer the use of informed consent documents took place in Cuba in the earlier 1900s, when U.S. Army physician Walter Reed (1851–1902) sought to establish the cause of yellow fever. Yellow fever had been a major public health problem in the Caribbean and Central America that killed thousands of people each year and threatened commerce and military operations. Reed's experiments helped to establish that *Aedes aegypti* mosquitos carry yellow fever, which was a major breakthrough in preventing the disease. To prove that the mosquito was the cause, Reed asked participants who had never had yellow fever to allow themselves to be bitten by mosquitos that had fed on patients with active yellow fever, or to be injected with blood from a yellow fever patient (Lederer 2008). Reed asked the volunteers to sign informed consent documents stating that they understood the risks of the experiment (including the possibility of death) and agreed to participate. The documents were translated into Spanish. Participants received $100 in gold and additional $100 and free medical care if they contracted yellow fever (Lederer 2008). Family members of participants who died also received $100. Two of his collaborators, James Carroll and Jesse Lazear, volunteered for the experiment. They both developed yellow fever and Lazear died. Reed had been planning to also volunteer for the experiment but Carroll talked him

Fig. 2.3 Walter Reed (Source: Wikimedia Commons, Public Domain. https://commons.wikimedia.org/wiki/File:WalterReed.jpeg)

out of it due to his age (the disease was more deadly for patients over 40 years old, such as Reed). A total of 33 volunteers participated in the experiment, including 18 Americans (2 civilians and 16 soldiers) and 15 Spanish immigrants. Six people died from yellow fever (Lederer 1995). The participants in the experiments were regarded as martyrs and heroes. The surviving military personnel received medals and government pensions, and the Army's Medical Center in Washington, DC was named after Reed (Lederer 1995) (Fig. 2.3).

It is not entirely clear why Reed asked the volunteers to sign consent documents, but the medical community's harsh reaction to Sanarelli's experiments probably influenced his decision-making (Lederer 2008). In any case, it is worth remembering that Reed used consent documents long before they became commonplace in medical practice and research in the 1970s. In 1822, William Beaumont (1785–1853) asked his patient Alexis St. Martin, to sign a document which some have regarded as a consent form, but it was more like an employment contract (Lederer 2008). St. Martin had been shot in the abdomen at close range. Beaumont tried to close the wound, but did not succeed. Beaumont, who saw a unique opportunity to observe digestive processes, asked St. Martin's permission to take samples of his digestive fluids, place food in the opening, and record internal body temperatures. In exchange for his cooperation, St. Martin received $150 for one year's employment as a Beaumont's personal servant. Beaumont also provided St. Martin with food, clothing, and lodging (Lederer 2008).

By the early twentieth century, physicians had mixed views about medical research. Physicians still accepted the Hippocratic ethos, but they were also interested in advancing medical science and testing new therapies. Although some physicians, such as Reed, sought consent from their patients, medical practice was highly paternalistic. Physicians often treated their patients without explaining what they were doing or why. They were more concerned with helping their patients than

obtaining consent and they often viewed medical experimentation as a necessary part of treatment. Indeed, physicians practicing medicine during this era did not have a clear sense of the difference between research and treatment and many mixed the two together (Lederer 1995).

In 1900, Prussia became the first nation to adopt legal rules concerning medical research. The Prussian Directive required medical researchers to obtain informed consent from their subjects and barred physicians from conducting research on children. The Prussian Directive was adopted in reaction to abuses of research subjects, such as an experiment in which a physician pricked the eye of a patient with a needle contaminated by nodules from a patient with leprosy to determine whether a particular strain of bacteria he was studying causes the disease (Shamoo and Resnik 2015). The American Medical Association also recognized that physicians encountered some ethical dilemmas concerning medical research. For several decades the organization deliberated about developing a code of ethics for medical research on human subjects, but did not formally adopt a code until 1946 (Lederer 1995).

During this same period, the eugenics movement spread throughout Europe and the U.S. Eugenics was a social and political ideology based on Darwin's theory of evolution by natural selection (or "survival of the fittest"). The founder of eugenics, Francis Dalton (1822–1911) argued that "defective" individuals should be prevented from breeding and "superior" ones encouraged to breed to improve the fitness of the human population. By the 1930s, 28 U.S. states had passed laws mandating involuntary sterilization of "unfit" individuals, including those who were mentally ill or disabled, criminally insane, or psychopathic. Approximately 100,000 people were sterilized under U.S. eugenics laws (Proctor 1988). Prominent proponents of eugenics included British Prime Minister Winston Churchill (1874–1965), U.S. President Theodore Roosevelt (1858–1919), science fiction writer H.G. Wells (1866–1946), and even African American scholar and civil rights activist W.E.B. Dubois (1868–1963), who opposed racism but believed in encouraging the most talented members of all races to interbreed.

German Chancellor and leader of the Nazi Party Adolf Hitler (1889–1945), who spoke favorably of America's eugenics laws in *Mein Kampf*, led Germany's eugenics movement (Proctor 1988). Inspired by the idea that Aryans constitute a "master race," Germany began in the 1930s a program of racial/ethnic purification to rid the country of "undesirable" members of the population, including Jews, mentally or physically disabled people, Gypsies, and mixed-race children. The program began after Hitler came to power in 1933, with the enactment of mandatory sterilization laws and it soon included "euthanasia" of mentally or physically disabled people. Approximately 250,000 people died in Germany's "euthanasia" program. Racial purification expanded to include segregation, forced labor, confiscation of property, imprisonment of Jews and others in concentration camps, and eventually to systematic genocide. Approximately six million people were killed in Germany's racial purification program, most of whom were Jewish concentration camp prisoners (Weindling 2008).

2.2 Research with Human Subjects During World War II

Coerced experimentation on Jewish concentration camp prisoners (and other "undesirables") was a natural outgrowth of the ideology behind racial purification. In Nazi Germany, Jews did not have the same rights as other people, such as the right to refuse to participate in dangerous experiments. The Nazi experiments are among the worst ever performed on human subjects. Some of these included (Proctor 1988; Weindling 2008):

- Exposing research subjects to freezing cold temperatures, extremely low pressures, and high levels of electricity and radiation to study their effects on the human body;
- Inflicting wounds on human subjects to study wound healing (subjects were shot, stabbed, or injected with metal or glass);
- Intentionally exposing human subjects to malaria, staphylococcus, tetanus, and other infectious diseases to study the effectiveness of vaccines;
- Injecting dye into human eyes to try to change eye color (many subjects went blind);
- Josef Mengele's (1911–1979) twin studies, which included forcing fraternal twins to have sex, mixing the blood of identical twins, sewing twins together to produce conjoined twins, and placing one member of a pair of identical twins in isolation from birth to study the role the environment in human development.

None of these experiments involved informed consent. The experiments killed, maimed, or permanently disabled thousands of people. Although most of these experiments were conducted by German military physicians or scientists, some were conducted by civilians. Although many of these experiments did not produce useful results, due to their poor design, some did, and researchers have debated about whether to use or cite Nazi data (Post 1991). Even today, the full extent of these experiments is not known, and many have come to light in recent years as a result of historical scholarship (Weindling 2008).

Less well-known are the Japanese chemical and biological warfare experiments on Chinese prisoners of war, which took place on mainland China from 1932 to 1945. These experiments did not gain much notoriety until the 1990s because the U.S. government was interested in the data from these experiments. The government agreed to refrain from prosecuting the researchers for war crimes in exchange for the data. In addition to testing chemical and biological weapons on human subjects, Japanese researchers also exposed human subjects to extremes of temperature and pressure, and conducted wound-healing, vaccination, and surgical studies involving people. Some studies also involved vivisection of human beings. Thousands of people died in the Japanese experiments (Tsuchiya 2008).

At the end of World War II, the Allied Powers put German military and political leaders on trial at Nuremberg, Germany for war crimes. Among these were the Nazi scientists and physicians who conducted experiments on human beings. Since the actions of the Nazi researchers were legal in Germany, the Nuremberg judges

needed a source of international law to serve as a basis for prosecuting the defendants. The War Crimes Tribunals adopted the Nuremberg Code (1949) to serve as a basis for prosecuting Nazi researchers for war crimes. The Code became the first internationally recognized ethical standard for research with human subjects (Capron 1989). The first principle of the code states that "the voluntary consent of the human subject is absolutely essential (Nuremberg Code 1949)." Other principles require that human experiments should benefit society and that experiments should be well-designed, minimize physical and mental risks to subjects, and be conducted only by qualified personnel. Subjects should be free to stop the experiment at any time (Nuremberg Code 1949).

2.3 Research with Human Subjects After World War II

After the Second World War, one of the next important events involving research with human subjects was the development of the polio vaccine. Polio (poliomyelitis) had been one the most feared childhood diseases, killing or permanently disabling thousands of people in the U.S. each year. The incidence of the disease had risen to 28.3 per 100,000 people by 1949 and 37.2 per 1000,000 by 1952. In 1952, polio killed 2500 people. Polio outbreaks led to school closings, quarantines, and other measures designed to prevent the spread of the disease (Meldrum 2008). Research on a polio vaccine took place in the 1930s, with little success. In the late 1940s, the National Foundation for Infantile Paralysis (NFIP), nicknamed the March of Dimes for millions of contributors giving a dime to the cause, began sponsoring research on a polio vaccine. In 1953, the Foundation announced it would conduct field trials of a vaccine, led by Jonas Salk (1914–1995). The NFIP decided to conduct a blinded randomized controlled trial (RCT), with an experimental group of second grade children receiving the vaccine and first and third grade children receiving a placebo. The researchers collected data on the incidence of polio in these two populations. This was the first RCT conducted on healthy children (Meldrum 2008). In 1953, the field trials began. Informed consent was obtained for the study via a letter sent home to the children's parents. U.S. counties with the highest incidence of the disease with more than 50,000 people were targeted for recruitment. 455,474 children (60.8% of the eligible population) participated in the study, 401,974 completed the full series of injections. On April 12, 1955, the researchers reported the results of the study in the *American Journal of Public Health*. The study was an overwhelming success: the vaccine was 80–90% effective at preventing the disease. Soon a massive vaccination campaign began. By 1956, 75% of children, ages 5–12, had received the vaccine. In 1957, the incidence of polio dropped to 3 per 100,000 (Meldrum 2008).

Although the polio vaccine clinical trial was a major victory in the fight against childhood diseases, it did raise some ethical concerns. The NFIP solicited a great deal of advice on scientific and ethical issues from investigators, physicians, and public health officials. Some were concerned about the safety of vaccine. Although

the vaccine used a dead virus, it was possible that in some batches might still contain live viruses. Some argued that the vaccine should be tested on a smaller group before launching a large field trial. However, the investigators were responding to an urgent need to develop a vaccine to deal with the epidemic, and testing it a smaller group first would have delayed the launch of larger study. Others worried that the parents were not fully informed of the risks of the vaccine and that their fear of polio compromised their ability to weigh risks and benefits (Meldrum 2008).

In 1964, the World Medical Association (WMA) met in Helsinki, Finland to draft an ethics code which is known as the Helsinki Declaration. The Declaration has been amended nine times since then, most recently in 2013 (World Medical Association 2013). The original version of the Declaration expanded upon the principles of Nuremberg Code and included 22 principles for ethical medical research. The Declaration addressed topics not covered by the Code, such as obtaining informed consent for legally incompetent subjects (such as children) and the use of control groups in clinical research. The Declaration prohibited the use placebo control groups when there is a known effective therapy (World Medical Association 1964). As noted in Chap. 1, the most recent version of the Declaration allows placebo control groups when there is a known effective therapy if subjects receiving a placebo do not face a risk of serious or irreversible harm (World Medical Association 2013). The preamble of the Declaration emphasized the importance of acting in the patient's best interests and stated that "the interests of science and society should never take precedence over considerations related to the well-being of the subject (World Medical Association 1964)." The most recent version of the Declaration includes a similar statement: "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects (World Medical Association 2013)."

After the Clinical Center of the National Institutes of Health (NIH) opened in 1953, researchers began informally reviewing human studies to minimize risks and unusual hazards. In 1965, the NIH formalized this process and required prior review of intramural human studies. In 1966, the NIH extended this prior review requirement to include extramural research. In 1971, the Food and Drug Administration (FDA) issued similar rules for human studies that generate data submitted to the agency (Capron 1989). These peer review committees were precursors to institutional review boards (IRBs).

In 1966, Henry Beecher (1966) published an article in the *New England Journal of Medicine* describing 22 studies involving human subjects which that he labelled as unethical. Research mentioned in the article included the Tuskegee Syphilis Study, the Willowbrook hepatitis experiments, and the Jewish Chronic Disease Hospital case. The article helped to raise awareness among clinical researchers of the importance of ethics, but did not lead to any immediate changes in government policy (Figs. 2.4 and 2.5).

The Willowbrook hepatitis research took place from 1956 to 1980 at the Willowbrook State School for Mentally Retarded Children in New York. Saul Krugman (1911–1995) supervised these experiments, which involved infecting healthy children with a mild form of viral hepatitis which was endemic at

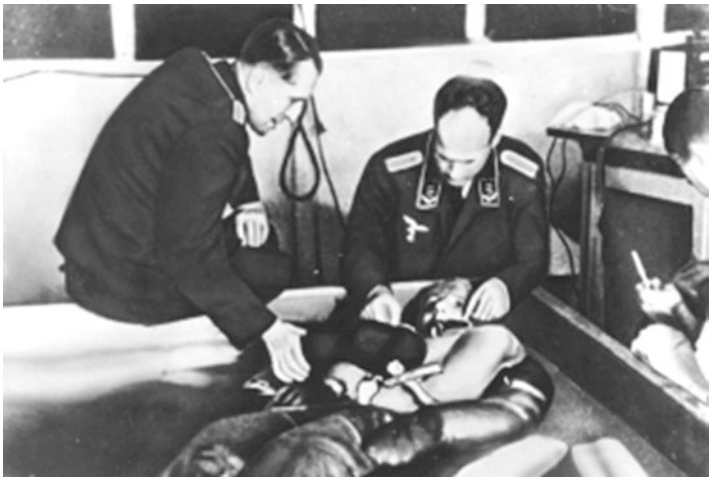

Fig. 2.4 Cold water immersion experiment on a Dachau concentration camp prisoner (Source: Wikipedia. Licensed under Fair use via Wikipedia – https://en.wikipedia.org/wiki/File:Dachau_cold_water_immersion.jpg#/media/File:Dachau_cold_water_immersion.jpg)

Fig. 2.5 Tuskegee syphilis study doctor injecting a subject (Source: Wikipedia, originally from National Archives. Licensed under Public Domain via Commons – https://commons.wikimedia.org/wiki/File:Tuskegee-syphilis-study_doctor-injecting-subject.jpg#/media/File:Tuskegee-syphilis-study_doctor-injecting-subject.jpg)

Willowbrook to determine whether this would provide them with immunity. The study included an experimental group, which received the virus prior to being admitted to the institute, and a control group, which did not receive the virus. The researchers obtained written informed consent from the parents. Several committees,

Fig. 2.6 Salk headlines. March of Dimes, licensed under Public Domain via Commons – https://commons.wikimedia.org/wiki/File:Salk_headlines.jpg#/media/File:Salk_headlines.jpg

including the New York State Department of Mental Health, approved the study. Over 700 children participated in the research. While the investigators' rationale for infecting healthy children with viral hepatitis was to develop a vaccine that could benefit other children, they also argued that the research subjects would benefit from their participation because they were likely to develop the disease within 6–12 months of staying at Willowbrook, and they would receive better medical care if they were intentionally infected and treated quickly, instead of becoming infected naturally, with treatment possibly delayed. Also, infected subjects would likely have immunity to the disease. Critics of the studies, including Beecher, argued that the study design and consent process were unethical (Robinson and Unruh 2008) (Figs. 2.6 and 2.7).

In 1963, Chester Southam and Deogracias Custodio injected live cancer cells into 22 debilitated patients at the Jewish Chronic Disease Hospital in Brooklyn, New York. The purpose of this research, which was funded by the American Cancer Society and the Public Health Service, was to better understand whether the immune deficiencies of cancer patients are due to their disease or their debilitation. The investigators did not tell the patients they were injecting them with cancer cells and they did not obtain written informed consent. They argued that there was no need to inform the patients that they were receiving cancer cells because they were likely to reject the foreign tissue, and so this posed very little risk to them. As it turned out, all patients, except those who died from their disease, rejected the cancer cells (Arras 2008).

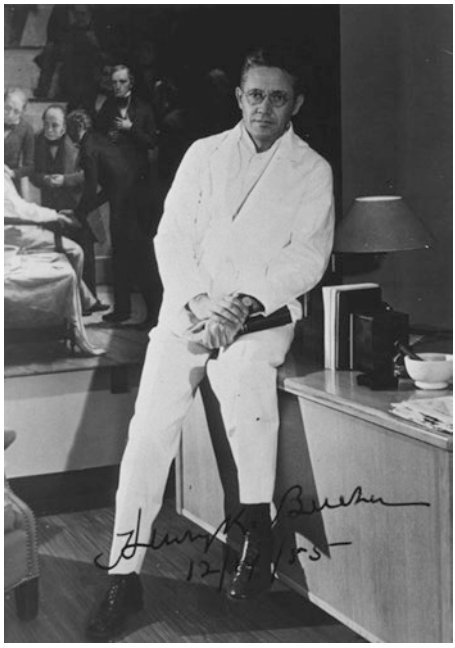

Fig. 2.7 Henry K. Beecher (Source: National Library of Medicine (public domain))

A behavioral experiment conducted by Stanley Milgram in the 1960s generated ethical controversy. The experiment, which had several variations, involved three types of participants: the learner, the punisher, and the researcher. In these experiments, electrodes were attached to the learner. If the learner answered a question incorrectly, the researcher instructed the punisher to press a button on a machine that would deliver an electric shock to the learner. The learners would wince or cry in pain upon receiving the shock. Punishers continued to administer electric shocks even when the meter on the machine indicated that the shocks were at a dangerous level. In some cases, punishers continued to administer shocks despite learners' demands to stop the experiment. In reality, no one received a shock, but the punishers did not know this until the experimental session concluded. The purpose of the study was to determine the extent to which human beings would obey an authority figure (the researcher), even when they were ordered to do something they considered to be morally wrong. Milgram considered this to be an important topic to study, since many German soldiers and prison guards during World War II defended their immoral actions by claiming that they were following orders. The experiment would not work if the learners had been told what was really happening, because this would not test their willingness to obey authority. During the debriefing after the experimental sessions, many of the punishers expressed a deep sense of regret that they were willing to do something they considered to be wrong. Some also objected to the deception and the experimental manipulation of their behavior (Milgram 1974).

The Tuskegee Syphilis Study took place in health clinics in Tuskegee, AL from 1932–1972. The purpose of this research, which was funded by the Department of Health, Education, and Welfare (DHEW), was to better understand the etiology of late-stage syphilis in African American men. The scientific rationale for this study was that this disease had been well-studied in whites but not in blacks, and it was important to be able to identify the signs and symptoms of this disease in this population. Because treatment for syphilis would interfere with observation of its natural course, 399 subjects in the "experimental" group did not receive treatment for syphilis. Subjects without syphilis constituted the "control" group for the study. The study was initially planned to last only a year, but it went on for decades. Subjects were not told that they were in an experiment nor offered treatment for syphilis when it became available in the 1940s (Jones 1981). Subjects thought they were receiving treatment for "bad blood." The "treatment" involved nothing more than medical examinations and routine care. Investigators steered subjects away from clinics where they might receive treatment for syphilis. The participants received free lunches and burials. The study did not receive national attention until Peter Buxton, a Public Health Service employee, informed the Associated Press about the research in 1972. The study was stopped shortly thereafter. Surviving research subjects and families of the deceased filed a class-action lawsuit against the U.S. government, and the parties agreed to a settlement in 1973. President William Clinton issued an official apology on behalf of the U.S. government to survivors and the families in 1997 (Shamoo and Resnik 2015).

2.4 The Belmont Report

Public outrage over the Tuskegee study led to Congressional hearings on the ethics of research with human subjects and passage of the National Research Act in 1973 (signed into law in 1974). The Act authorized federal agencies to draft regulations for research involving human subjects and created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Shamoo and Resnik 2015). In 1978, the DHEW announced revisions to its regulations for research with human subjects. In 1979, the National Commission issued the *Belmont Report*, which provided an ethical framework for research involving human subjects that served as a conceptual foundation for a major revision of federal regulations in 1981 (National Commission 1979).

The *Belmont Report* described the principles for ethical research involving human subjects: respect for persons (which requires informed consent from research subjects as well as additional protections for those who cannot consent); beneficence (which requires maximization of the benefits of research and minimization of risks); and justice (which requires fair distribution of benefits and burdens of research). The authors of the report did not say what makes a distribution "fair" other than to list some different ways of distributing benefits and burdens. The authors acknowledged that the principles may sometimes conflict and that to make

an ethical decision concerning research with human subjects one must balance these different principles in light of the relevant facts and circumstances (National Commission 1979).

The *Belmont Report* also distinguished between medical therapy and medical research. The goal of therapy, according to the authors of the *Report*, is to benefit the patient, whereas the goal of research is to produce generalizable knowledge (National Commission 1979). The authors of the *Report* argued that it is important to distinguish between research and therapy to determine what types of activities should be regulated as research. They also noted that research and therapy often occur concurrently but that if any part of a medical intervention involves research it should be regulated as such. The authors also noted that innovative medical practices do not need to be regulated as research but they encouraged physicians to develop research protocols to evaluate them (National Commission 1979).

The authors of *Belmont Report* stressed the importance of protecting research subjects who are vulnerable, due to their compromised ability to provide consent or their dependency on others. The authors said care should be taken to avoid unjustly using vulnerable individuals as research subjects solely for administrative convenience or because they are easy to manipulate due to illness or their socioeconomic circumstances (National Commission 1979). The authors also said the justice requires that there should be a preference in the order of selection of research subjects, i.e. adults should be preferred to children for research that is not on exclusively pediatric conditions and some subjects, such as prisoners or mentally disabled people, should be used only under special circumstances (National Commission 1979).

The twelve-page *Belmont Report* has become one of the most influential documents pertaining to research with human subjects. It is frequently cited in books, articles, government reports, and official guidance. Also, many institutions agree to follow the ethical principles of the report when they sign an agreement (known an as an assurance) to receive federal funding for research with human subjects (Shamoo and Resnik 2015).

Despite its considerable influence, the *Report* has some flaws. First, the principles summarize some key insights from ethical theories and traditions, but the *Report* itself does not examine these principles or their underlying philosophical justification in any depth (Beauchamp 2005). Second, as noted earlier, the *Report* does not include a decision-procedure for prioritizing the principles when they conflict. Third, although the *Report* includes some applications of the principles, none of these provide details concerning real or hypothetical studies. Consequently, one is left wondering exactly how to apply the principles to situations and resolve conflicts (Veatch 2005).

2.5 The U.S. Federal Regulations

In 1981, federal agencies announced major revisions to their regulations for protecting human subjects in research. The regulations include the Common Rule, i.e. regulations adopted by 17 federal agencies, and the FDA regulations, which apply to research submitted to the agency for approval of products under its jurisdiction (Department of Health and Human Services 2009; Food and Drug Administration 2010, 2013).[1] The regulations were revised again in 1991 and in 1996 (FDA only), with a minor revision to the Common Rule in 2009. Major revisions to the Common Rule were announced in January 2017 (Department of Homeland Security et al. 2017). Chapter 11 will discuss these revisions in more depth. Since the Trump Administration may make changes to these revisions or delay their implementation, unless noted otherwise, all references are to the 2009 version of the Common Rule. The Environmental Protection Agency (EPA) also has regulations (discussed below) for research submitted to the agency by private companies for EPA-sponsored research involving children or pregnant/nursing women that differ from the Common Rule (Resnik 2012a).

There are a few significant differences between the FDA regulations and the Common Rule. For instance, the Common Rule allows the IRB to waive informed consent under certain conditions, but the FDA regulations require that consent be obtained and documented unless research is conducted under the emergency research rules (FDA 2010).[2] However, for the most part the FDA regulations track the Common Rule's provisions concerning institutional review boards (IRBs), review criteria, and institutional oversight (Shamoo and Resnik 2015).

Sub-part A of the Common Rule sets forth general requirements for research with human subjects, while sub-parts B-D address special requirements for research involving pregnant women, fetuses, and neonates; children; and prisoners (Department of Health and Human Services 2009). The regulations establish a system of institutional oversight of research involving human subjects. Institutions[3] are required to provide the agency with a written assurance that they will follow the regulations; designate one or more IRBs to review research and provide space and staff support for the IRB; provide the agency with a list of IRB members and their qualifications; establish standard operating procedures (SOPs) for IRBs to follow; and establish procedures for reporting to IRBs, institutional officials, and the agency unanticipated problems involving risks to subjects or others and serious or continuing noncompliance with federal regulations or IRB determinations (Department of Health and Human Services 2009, 45 CFR 46.103).

The IRB is the locus of institutional oversight. IRBs have the authority to approve, disapprove, require changes to, audit, suspend, or terminate research (45

[1] FDA regulated products include drugs, biologics, and medical devices.

[2] The FDA's emergency research rules will be discussed in Chap. 5.

[3] The 2017 version of the Common Rule shifts some of these responsibilities to IRBs (Department of Homeland Security et al. 2017).

CFR 46.109, 45 CFR 46.113). IRBs are required to notify investigators in writing of their decisions; conduct continuing reviews of previously approved studies no less than once a year; and keep records of meeting minutes, research proposals, consent forms, SOPs, and communications with investigators; (45 CFR 46.109, 45 CFR 46.115). IRBs shall include at least five members of varying backgrounds, with at least one member not affiliated with the institution and at least one non-scientist member. IRBs should include members who are qualified to provide the board with advice concerning scientific, professional, ethical, and legal issues and community perspectives. IRBs should include members of different genders and different races/ethnicities (45 CFR 46.107). If an IRB regularly reviews research on vulnerable subjects it should include members who have knowledge and expertise concerning these categories of subjects. An IRB may invite outside, non-voting experts to assist with its decision-making. If an IRB member has a conflict of interest[4] related to a study, he or she may provide information about it to the board but cannot vote (45 CFR 46.107). Institutions that work together on research may agree to rely on one IRB to avoid duplication of effort (45 CFR 46.114).[5] Some institutions contract out IRB review and oversight to private IRBs (Emanuel et al. 2006).

To approve a proposed study, an IRB must determine that it meets all the following criteria:

1. Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
3. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

[4] For example, an IRB member who is an investigator on a study being reviewed by the board would have a conflict of interest.

[5] These agreements are known as reliance agreements or authorizations.

4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects (45 CFR 46.111).

An IRB must also determine that a study continues to meet these requirements when it conducts continuing review or approves an amendment to an approved study.

The Common Rule includes informed consent requirements.[6] Investigators should seek consent in circumstances that minimize the potential for coercion or undue influence and give the subject (or his or her legal representative) an opportunity to decide whether to participate in the study (45 CFR 46.116).[7] Consent should take place in language understandable to the subject and should not include legally exculpatory language in which the subject waives or appears to waive legal rights (45 CFR 46.116). The Common Rule also spells out the types of information that investigators are required to share with subjects, including: a statement that study involves research; a description of the research, including its purpose, procedures, risks and benefits; the duration of the subject's participation; alternatives to participation; confidentiality protections; a statement that participation is voluntary and that the subject can refuse to participate or stop participating with penalty or loss of benefits to which he or she is otherwise entitled; information about whom to contact to answer questions about the research or in case of injury; and, for more than minimal risk research, a statement concerning whether compensation or treatment for injury is available (45 CFR 46.116a).

The regulations also include provisions for waiving informed consent requirements. For example, an IRB can waive consent requirements if it finds that (1) the research is no more than minimal risk, (2) it would be impractical to conduct the research without a waiver, (3) investigators will provide pertinent information to the subject after the research ends (if appropriate), and (4) the waiver will not adversely affect the subject's rights or welfare (45 CFR 46.116d).

[6] Additions to these requirements will be discussed in Chap. 11.

[7] A legal representative might include a parent, guardian, health care agent, or close family member, depending on the circumstances and local laws.

The regulations also include consent documentation requirements and allow the IRB to waive these requirements for some types of research deemed to be no more than minimal risk (45 CFR 46.117).[8]

The Common Rule includes some procedures for reducing administrative burden on the IRB and investigators and restricting the IRB's authority. First, the Common Rule includes procedures for expedited review. An IRB can use an expedited review procedure to review a new research project judged to be minimal risk, for continuing review of a previously approved study that is minimal risk or is no longer recruiting subjects or collecting data, or for minor changes to an approved protocol. Under expedited review, the IRB chair or another knowledgeable IRB member performs the review, instead of the full board (45 CFR 46.110).

Second, the Common Rule includes some categories of research deemed to be exempt from IRB review, such as some types of studies involving educational methods or tests, surveys, interviews, or observations of public behavior; or research on previously existing samples or data in which the recipients will not have access to personally identifying information (45 CFR 46.101).[9] Most institutions require investigators who are planning to do research that would qualify as exempt to submit a short form to the IRB describing the research (Shamoo and Resnik 2015).

Third, many activities involving collection of human samples or data are not subject to IRB review because they do not qualify as research on human subjects. A human subject is a living individual whom the researcher obtains data from by interacting with the individual or accessing their private information, and research is a systematic attempt to develop generalizable knowledge (45 CFR 46.102).[10] For example, if a hospital conducts a quality improvement project pertaining to its own activities only, this would probably not be reviewed as research because it would not be a systematic attempt to develop generalizable knowledge. Likewise, medical therapy should not be reviewed as research unless it also includes activities that qualify as research.

In addition to the general considerations related to protecting vulnerable subjects mentioned in 45 CFR 46.111, the Common Rule also includes protections for specific classes of vulnerable subjects.[11] Sub-part B allows IRBs to approve three types of studies involving pregnant women or fetuses: (1) research with the potential to directly benefit the woman or her fetus; (2) research not expected to benefit the women or fetus but which poses no more than minimal risk to the woman or her fetus; and (3) research that is expected only to benefit the fetus. For each of these categories, consent of the woman must be obtained; for the third, consent of the father also must be obtained, if he is available. If the woman is a child, consent must be obtained from her parent(s) or guardian(s) and she must give her assent (45 CFR 46.204). Sub-Part B permits research to be conducted on neonates of uncertain viability only if the research has the potential to enhance the survival or the neonate

[8] Chapter 5 will discuss documentation requirements in greater depth.

[9] Chapter 11 will discuss changes to exempt research adopted in 2017.

[10] Chapter 11 will discuss a minor change to this definition adopted in 2017.

[11] Chapter 9 will focus on ethical issues in research with vulnerable subjects.

and minimizes risks; or, if the research is not likely to enhance the survival of the neonate, it must not impose any additional risks on the neonate. Research on a non-viable neonate is permitted if vital functions will not be maintained artificially, the research will not terminate heartbeat or respiration, and the research poses no added risk to the neonate (45 CFR 46.205). Sub-Part B also describes a process for approving research involving pregnant women, fetuses, or neonates which is not otherwise approvable under these three categories. The process involves submitting the research proposal to the agency head, formation of an expert panel, and public comment (45 CFR 46.207).

Sub-Part C allows four types of research to be conducted on prisoners: (1) minimal risk research on the causes and effects of incarceration and criminal behavior; (2) minimal risk research on prisons as institutional structures or on prisoners as incarcerated people; (3) research on prisoners as a class; and (4) research which has the prospect of directly benefitting the subject (45 CFR 46.306). Sub-Part C also requires that an IRB which reviews research on prisoners include a prisoner or prisoner representative, with the majority of non-prisoner board members having no association with the prison (45 CFR 46.304). The regulations also include a definition of a prisoner (45 CFR 46.303).

Sub-part D permits four types of research involving children: (1) research involving no more than minimal risk; (2) research involving more than minimal risk but with the prospect of directly benefitting the subject; (3) research involving only a minor increase over minimal risk and no prospect of direct benefit but likely to yield important knowledge concerning the subject's disorder or condition; and (4) research not otherwise approvable under the first three categories (45 CFR 46.404-407). Research under the fourth category involves submission of the proposal to the agency head, formation of an expert panel, and public comment (45 CFR 46.407). Sub-part D also includes requirements for obtaining consent from the parent(s)/guardian(s) and assent from the child, if appropriate. For research under the third and fourth categories, consent from both parents must be obtained, if they are available. The IRB may waive parental/guardian consent if it determines that consent is not a reasonable requirement, e.g. because the subjects are abused or neglected children (45 CFR 46.408).

"Minimal risk" is one of the most important terms used in the federal regulations because it defines certain types of approvable research under Sub-Parts B, C, and D as well as research approvable by expedited review (Shamoo and Resnik 2015). The federal regulations define minimal risk as: "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102i)." The definition of minimal risk for prisoners is "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons (45 CFR 46.303d)."

Federal agencies have the authority to assure compliance with their regulations. The Office of Human Research Protections (OHRP) and the FDA frequently issue letters concerning non-compliance to institutions, IRBs, sponsors, and investigators.

They also conduct random and for-cause audits. The agencies have also developed guidance documents for interpreting the federal regulations (Food and Drug Administration 2014; Office of Human Research Protections 2017). However, as mentioned in the Chap. 1, disputes still arise concerning the interpretation of the regulations (Shamoo and Resnik 2015).

2.6 Continuing Scandals and Controversies

Although the federal regulations helped establish ethical and legal standards for conducting research with human subjects, controversies and scandals continued to surface. Some of these have involved exposés of research conducted in the past. Congress held hearings in 1975 and 1977 on Central Intelligence Agency (CIA) secret mind control research, which took place from 1951 to 1973. The agency conducted human behavioral experiments using lysergic acid diethylamide (LSD), sodium pentothal, hypnosis, radiation, and electric shocks. The purpose of the research was to develop methods for obtaining information from someone, planting suggestions in someone's mind, and other forms of controlling thought or behavior (Goliszek 2003). These experiments, which often occurred without consent, involved dozens of human subjects. On November 19, 1953, CIA researchers gave LSD to unwitting human subjects. One of these victims, civilian army employee Frank Wilson, became paranoid, agitated, and severely depressed. Several days after taking LSD, Wilson died after jumping out a tenth floor window. Some of the "voluntary" CIA LSD experiments involved drug addicts who were serving prison sentences for drug violations. The researchers gave the subjects a variety of hallucinogenic drugs and observed them for several days. To pay them for their participation, the researchers provided the subjects with morphine, or any other drug they wanted, after the experiment was over (Goliszek 2003).

Ironically, declassified documents have revealed that Henry Beecher conducted secret experiments for the CIA on the use of LSD as an interrogation tool on unwitting human subjects from 1951 to 1952. Though Beecher would come to be regarded as a champion of ethical research after publishing a famous essay in the *New England Journal of Medicine* (see earlier discussion), he apparently conducted some unethical experiments before having a change of heart (McCoy 2007).

In 1994, the Clinton administration began declassifying thousands of documents pertaining to secret experiments sponsored by the U.S. government during the Cold War period (1944–1974). Many of these were human radiation experiments sponsored by the Department of Energy (DOE) or Department of Defense (DOD) involving approximately 4000 civilians or military personnel. The Clinton Administration appointed a national commission to review these experiments and determine whether they violated legal rules or ethical standards. Most of these experiments occurred after the international community had adopted the Nuremberg Code but before the U.S. had developed any human research regulations (Advisory Committee on Human Radiation Experiments 1995). Some of the survivors of these experiments

and families of the deceased filed a class-action lawsuit against researchers, institutions, and the U.S. government (In Re Cincinnati Litigation1995).

Investigators, government officials, and military leaders invoked a utilitarian rationale for this research: The U.S. needed to conduct radiation experiments to have a better understanding of how radiation affects human health to inform national security strategies related to a potential conflict with the Soviet Union (Goliszek 2003). Most of these experiments involved exposure to low doses of radiation, and did not entail any serious, long-term harm to subjects. However, some of the studies increased the lifetime cancer risk of the subjects, and some used children or pregnant women. Also, consent was not obtained in most of the studies (Advisory Committee on Human Radiation Experiments 1995). Some studies noteworthy for ethical problems include (Advisory Committee on Human Radiation Experiments 1995; Goliszek 2003):

- In the 1940s, researchers at Vanderbilt University gave radioactive iron pills to pregnant women to understand how radiation impacts fetal development;
- From the 1940s to the 1960s, the military exploded nuclear weapons or released radioactive fallout clouds in the South Pacific Islands, Utah, New Mexico, Nevada, and Washington State to study the impact of radiation on ecosystems, organisms, and human beings;
- From the 1940s to the 1960s, investigators injected radium into the noses of about 1500 military personnel, many of whom developed headaches and nosebleeds;
- From 1951 to 1956, researchers at the Texas M.D. Anderson Cancer Center administered total body radiation to 263 male cancer patients, many of whom experienced nausea, vomiting, or bone marrow depletion, to understand how radiation affects motor skills needed for flying aircraft;
- In the 1950s, researchers at Columbia University administered radioactive isotopes of calcium and strontium to patients with terminal cancer to understand how human bones and tissues absorb radioactive material;
- From 1963 to 1971, researchers at Oregon State Prison x-rayed the testicles of male prisoners (most of whom were African American) to understand how radiation affects sperm function.

In 2010, an experiment hidden from view for over 50 years came to light while Wellesley College professor Susan Reverby was conducting research on the Tuskegee Syphilis Study. When she was examining Public Health Service (PHS) records on the study she discovered another PHS study that took place between 1946 and 1948 in Guatemala. The study exposed 696 subjects to syphilis to determine whether taking penicillin prophylactically can prevent the disease. 427 of the subjects developed syphilis. To expose human subjects to syphilis, the researchers first asked prisoners to have sex with prostitutes who had the disease. When this method proved to be ineffective, they inoculated subjects' cheeks, forearms, and penises with syphilis. The researchers selected Guatemala for the study site, in part, because they knew they would have trouble getting permission for some of their research activities (such as subjects having sex with prostitutes) in the U.S. After

Reverby published her findings, President Barack Obama issued an official apology to the Guatemalan government and asked his Presidential Commission for the Study of Bioethical Issues to investigate the incident and review U.S. human research protections to ensure that nothing like this could happen again (Semeniuk and Reverby 2010).

During the 1990s, pharmaceutical companies began conducting clinical trials in developing nations. Although some companies were genuinely interested in helping address public health problems that were of concern to local populations, others moved studies to developing countries to save money on labor and avoid regulatory burdens. At that time, most developing nations had no laws, regulations, or guidelines concerning the conduct of research with human subjects. Ethicists and human rights activists became concerned that pharmaceutical companies were exploiting human participants and local populations in developing nations by not providing them with substantial benefits (Hawkins and Emanuel 2008).

In 1996, Pfizer conducted a study in Nigeria that confirmed some of these charges of exploitation. Pfizer was responding to an epidemic of meningitis in Africa which would eventually kill over 15,000 people. The company enrolled nearly 100 children in a clinical trial of Trovan, an experimental meningitis drug that had never been tested in children. The children were randomly assigned to two groups, one which received Trovan and another which received a medication commonly used to treat the disease. While there is no evidence that the children suffered additional, significant harm from participating in the study—5 died in the Trovan arm of the study and 6 died in the comparator arm—there is also no evidence that the parents provided consent for the study or knew their children were participating in an experiment. Also, Pfizer did not obtain proper ethics approvals for the study. Parents of the children sued Pfizer and eventually won an out-of-court settlement. In 1997, the FDA had approved the Trovan for use in adults but not children and restricted use of the drug, based on evidence that it increased the risk of liver damage and death (Stephens 2006).

In 1998, the Environmental Working Group published a report accusing chemical companies of conducting unethical pesticide experiments on human subjects. The experiments involved administering low doses of pesticides to healthy human subjects to determine whether they produce adverse at effects at these exposure levels. In most of these experiments, human subjects ingested small quantities of pesticides. The researchers collected biological samples from the subjects to measure pesticide metabolite levels in the blood and urine and biochemical indicators of toxicity. Many of the subjects were college students who were paid as much as $470 for their participation, but some were company employees (Resnik 2012a). Critics said that the studies were scientifically and ethically flawed because: (1) sample sizes were too small to generate valid data; (2) company employees were research subjects in some cases, which was potentially coercive; (3) appropriate measures to minimize risks were not implemented; (4) data gathered on adults were not relevant to pediatric risks; and (5) the results were not likely to yield useful information for society because the health risks of the pesticide exposures were already well-understood (Lockwood 2004).

The companies conducted these experiments to generate data to submit to the Environmental Protection Agency (EPA) to convince the agency to increase allowable levels for these chemicals on foods. Congress passed the Food Quality Protection Act (FQPA) in 1996 to require the EPA to implement more stringent safety standards for pesticide residues on food. Prior to the adoption of the FQPA, the EPA regulated allowable pesticide residue levels on foods using two safety factors of ten, one to account for variations between animals and humans and another to account for variations among humans. The FQPA mandated an additional safety factor of ten to protect children from exposure risks, i.e. an allowable exposure of 1/1000 of the level which produces no adverse effects in rodents. The companies hoped that their data would convince the agency to modify the other safety factors (Resnik 2012a).

The EPA had adopted the Common Rule for studies sponsored by the agency but did not have any regulations for studies conducted by private companies (third parties). The agency had accepted third party data on a case-by-case basis, applying relevant ethical and scientific criteria to the research. In 1998, the EPA asked the National Research Council (NRC) to study the ethical and scientific issues related to testing pesticides and other toxic chemicals on human subjects and announced that it would not accept any third party human data until the NRC released its report. Pesticide manufacturers sued the EPA on the grounds that it had engaged in unlawful rulemaking because it had not given proper notice or taken public comments prior to making the decision to no longer accept third party human data. In 2003, a federal court ruled in favor of the plaintiffs and ordered the EPA to engage in appropriate rulemaking for third party human subjects research.

By 2004, environmental groups, environmental researchers, ethicists, and members of the public had raised serious concerns about testing pesticides on human subjects. Some argued that privately funded human pesticide testing was inherently unethical and should never be performed (Stokstad 2005). In February of 2004, the NRC issued its report on experiments that involve testing pesticides or other toxic chemical on human subjects. The report said that these types of experiments were acceptable if they meet stringent scientific and ethical standards, such as good study design, informed consent, risk minimization, social value, and protection of vulnerable subjects. The NRC recommended that the EPA adopt the Common Rule for third party research (National Research Council2004). The EPA began to take steps to revise its human subjects regulations in accordance with the NRC's recommendations (Resnik 2007b).

In the fall of 2004 an observational study of children's pesticide exposures generated a controversy that would have a dramatic impact on the EPA's human subjects regulations. The study, named Children's Environmental Exposure Research Study (CHEERS), was sponsored by the EPA, Centers for Disease Control and Prevention (CDC), and Duvall County, Florida Health Department. The goal of the study was to observe children's exposures to pesticides and household chemicals in the home. The investigators planned to recruit sixty families with children living in the home, including a group with high pesticide use and a control group of families with low pesticide use (or no pesticide use). The study would include five home visits over a

two-year period. During the home visits, the investigators would collect biological samples from the children (blood and urine) and soil and dust samples from the home. Families would keep a journal of their pesticide and chemical use and videotape their children's activities. For their participation, parents would receive $970 and t-shirts, and they would be allowed to keep the camera used for videotaping. Investigators and the sponsors regarded the study as important for promoting children's health because little was known about children's exposures to pesticides and other chemicals in the home. The American Chemistry Council (ACC) contributed $2 million to the study, but it had no role in designing the research or interpreting the results. IRBs and peer review committees from the EPA, CDC, and Duvall County Department of Health approved the study and classified it as minimal risk (Resnik and Wing 2007).

Before the study could get off the ground, a controversy erupted. Environmental groups, human research ethics groups, and journalists portrayed CHEERS as an intentional exposure study that would use children as "guinea pigs." This impression was mistaken because the study had an observational, rather than experimental design. However, some were concerned that parents might intentionally expose their children to pesticides to enroll in the high use group in the study. To prevent this from happening, the investigators planned to make an initial screening visit to the home immediately after enrolling a family in the study to determine the family's level of pesticide use. They also told families they were free to withdraw from the study at any time and could remain in the study even if they were in the high-use group and stopped using pesticides (Resnik and Wing 2007).

Another criticism of the study is that it was targeting low-income minority groups living in Duvall County. However, investigators selected the site because they knew that many families in the area were using large amounts of pesticides to control roaches and other pests. Race, ethnicity, and income were not part of the study's inclusion or exclusion criteria. Although the study did not target racial/ethnic minorities or low-income participants, it probably would have enrolled a disproportionate number of families from these groups (Resnik and Wing 2007).

Critics also argued that the amount of money offered to the parents was excessive and could induce them to enroll in the study against their better judgment, especially since it was likely that most of the parents in the study would be economically disadvantaged. However, the amount of money offered to the parents was probably a fair rate for their participation since the study involved considerable inconvenience and about 150 h of the parents' time.[12] The parents would receive $6.47 per hour, slightly above the federal minimum wage at the time of $5.15 per hour (Resnik and Wing 2007).

Although the EPA and CHEERS investigators attempted to defend the study against these criticisms, the controversy persisted. In the spring of 2005, California Representative Barbara Boxer and Florida Senator William Nelson threatened to block Stephen Johnson's nomination as EPA administrator if the agency did not study the study. The EPA surrendered to this political pressure and cancelled the

[12] Payments to participants will be discussed in more depth in Chap. 5.

study. Later that year, Congress passed a law prohibiting the EPA from sponsoring pesticide experiments on children or pregnant or nursing women. In 2005, the EPA adopted regulations that went beyond the requirements of the law. The regulations prohibit the agency from sponsoring any research that intentionally exposes children or pregnant or nursing women to chemicals, allergens, cosmetics, air pollution, or other environmental agents. These regulations are more restrictive than the Common Rule's protections for children and pregnant women, which allow such research if it is deemed to be minimal risk (Resnik 2007c).

2.7 Concerns About Integrity in Biomedical Research

In the 1990s there were growing concerns about integrity in biomedical research (and to a lesser extent in other types of research), due to some highly publicized cases of data fabrication and falsification in studies funded by the U.S. government as well as allegations of bias and conflict of interest (COI) in privately-funded research.[13] During that period, government agencies, including the National Institutes of Health (NIH) and National Science Foundation (NSF) developed policies pertaining to misconduct and conflicts of interest in research. Academic institutions were obliged to comply with these policies as condition of receiving funding. The FDA also developed COI policies for research it regulates and for its advisory committees. In 2001, the federal government finalized a policy that defines research misconduct as fabrication, falsification, or plagiarism. In 2005, the NIH strengthened its COI policies for intramural researchers, and in 2011, the NIH and NSF revised their policies for extramural researchers.[14] Scientific journals developed policies pertaining to research misconduct and disclosure of financial or other conflicting interests (Shamoo and Resnik 2015).

One of the misconduct cases with human subjects which made national headlines involved the NIH-funded National Surgical Adjuvant Breast and Bowel Project (NSABP). In 1993, University of Montreal professor of Surgery Roger Poisson admitted to altering medical records from 117 of his patients between 1977 and 1990 to enable them to qualify for enrollment. Poisson admitted wrongdoing after being investigated by his institution and the Office of Research Integrity (ORI). In defending his actions, Poisson claimed that he was trying to help his patients participate in a study which could benefit them. The ORI ordered Bernard Fisher, a University of Pittsburgh cancer researcher and NSABP chairman, to reanalyze the data to determine whether the falsification impacted the study's outcome. Fortunately, the reanalysis showed that Poisson's misconduct had no effect on the study's overall results. The study found that lumpectomies are just as effective as mastectomies at treating breast cancer tumors less than 4 cm wide. Although Fisher

[13] Research integrity will be discussed in more depth in Chap. 10.

[14] Intramural researchers are employed by the NIH; extramural researchers are employed by academic institutions that receive funding from the NIH for their research.

was never accused of misconduct, he resigned his position to appease Congress (which was investigating the incident) and the NIH. Fisher sued the government for damaging his reputation because the NIH had labelled 93 of his papers with a warning that misconduct was suspected (Resnik 2008a).

British surgeon Andrew Wakefield and 12 coauthors published a paper in *Lancet* in 1998 speculating that exposure to the measles, mumps, and rubella (MMR) vaccine can cause autism in children. The paper claimed that 12 healthy children developed gastrointestinal disease and developmental regression after receiving the vaccine. The paper had a negative impact on vaccination rates in the U.K. and other countries because the anti-vaccination community cited Wakefield's results as proof that childhood vaccinations cause autism. British journalist Brian Deer began investigating Wakefield's research. In 2004, Deer published an article in the *Sunday Times* claiming that Wakefield had not disclosed a significant financial interest and had not obtained ethics board approval for the study. Wakefield's research had been supported by a law firm that was suing vaccine manufacturers, and a lawyer for the firm had helped Wakefield recruit patients. Wakefield did not disclose his relationship to the law firm in the 1998 paper. In 2010, the U.K.'s General Medical Council (GMC) revoked Wakefield's license to practice medicine following an investigation which concluded that he had not disclosed a significant financial interest and had performed risky procedures, such as colonoscopies and lumbar punctures, without appropriate pediatric qualifications or ethics committee approval. *Lancet* retracted the paper shortly thereafter. Deer continued pursuing Wakefield. In 2011 he published an article in the *British Medical Journal* accusing the surgeon of fabricating and falsifying data in the 1998 paper. Deer reviewed the medical records of the children involved in the study and found that five of the children already had developmental problems before entering the study and that four of the children which Wakefield said had autism or developmental regression were healthy. Deer also found that the researchers had changed nine normal pathology results to colitis. Wakefield has denied these allegations and continues to advise anti-vaccine groups (Shamoo and Resnik 2015).

On March 17, 2005, University of Montreal professor Eric Poehlman admitted to fabricating or falsifying data on 15 federal grant applications (worth $2.9 million in funding) and 17 papers over a ten-year period as part of a comprehensive settlement dealing with criminal, civil, and administrative law charges against him. For several years, the University of Vermont (where Poehlman worked from 1987–1993 and 1996–2001) and the ORI had been investigating allegations of research misconduct against Poehlman made by Walter Denino, one of his research assistants. Denino found that Poehlman had changed some data points on Excel spreadsheets to support his hypotheses. In one study, most of the research subjects did not exist. During the investigation, Poehlman destroyed evidence and gave false testimony to investigators. Under the terms of the settlement, Poehlman agreed to pay $180,000 to the government and $16,000 to Denino's attorney. He also agreed to a lifetime ban on receiving federal research funding and to retract papers affected by his misconduct. Poehlman was also sentenced to serve one year and one day in federal prison for defrauding the government. He had published highly-cited papers on menopause,

metabolism, and aging. In his defense, Poehlman said he broke the rules of science because he felt significant pressure to obtain funding to keep his lab operating and support the salaries of his students and staff (Resnik 2008a; Shamoo and Resnik 2015).

Another episode of research misconduct involving human subjects made international headlines in December 2005, when Seoul University professor Woo Suk Hwang admitted to fabricating and falsifying data in two papers published in *Science* in 2004 and 2005, which described the derivation of human embryonic stem cell lines by therapeutic cloning.[15] Hwang had become a national hero in South Korea for bringing recognition to his country for its scientific accomplishments. Earlier that year, Hwang had been the first person to clone a dog (named Snuppy). Problems with the research began to surface when one of Hwang's collaborators, University of Pittsburgh stem cell researcher Gerald Schatten, said that Hwang had misled him about the source of human eggs used in the experiments. Contrary to what Hwang had told Schatten, some of the eggs had come from Hwang's laboratory technicians. Though this practice was legal in South Korea, many regarded it as unethical because it was potentially coercive. Hwang admitted that he helped the donors fill out some paperwork and that he paid them up to $1400 for their eggs. Allegations of research fraud emerged when Sung Rho, one of Hwang's collaborators, informed the media that Hwang had fabricated 9 out of 11 images of cell lines in the 2005 paper. An investigation by Seoul University found that all of the images of cell lines in the papers had been fabricated or falsified, and that Hwang had used 273 eggs, not the 185 he had reported. In May 2005, a South Korean court convicted Hwang and five collaborators of fraud and embezzlement (totaling $3 million), but the court suspended their sentence (Shamoo and Resnik 2015).

During the 1990s, financial ties between academic scientific researchers and private companies expanded. Private companies (especially pharmaceutical and biotechnology companies) boosted their funding for academic scientific research, continuing medical education, and other forms of financial support for universities and medical centers. Researchers increasingly reported financial relationships to private sponsors, such as stock ownership, and receipt of fees for consulting or speaking. Researchers also began more aggressively pursuing intellectual property related to their work (such as patents) and formed start-up companies (often with institutional support) to commercialize their discoveries and inventions. Academic institutions also became more entangled with industry via ownership of stock or intellectual property, licensing of intellectual property, and receipt of donations from private companies. Academic institutions formed technology transfer offices to manage their intellectual property and help researchers commercialize research, and created private foundations to hold stock and engage in corporate fundraising (Krimsky 2003; Resnik 2007a).

[15] In therapeutic cloning, researchers transfer a nucleus from a patient's somatic cells into a zygote which has had its nucleus removed to produce embryonic stem cells which are virtually genetically identical to cells taken from the patient.

As these financial ties between academia and industry strengthened, scientists, ethicists, policymakers, and members of the public became increasingly concerned that the financial interests of private sponsors could threaten the objectivity and integrity of biomedical research. Researchers began to publish studies demonstrating relationships between sources of funding and financial interests and research results (Krimsky 2003; Bekelman et al. 2003; Sismondo 2008a). Researchers also published articles reporting that a significant percentage of industry-sponsored studies have "ghost authors," i.e. individuals who have made contributions to the study which meet authorship criteria but who are not named as authors. For example, Gøtzsche et al. (2007) found that 75% of studies reporting industry-sponsored clinical trials had ghost authors. Corporate sponsors sometimes use ghost authors to conceal financial interests and industry ties related to published research (Resnik 2007a).[16]

2.8 Jesse Gelsinger's Death

In 1999, a high-profile tragedy occurred which gave a human face to concerns about COIs in biomedical research. Jesse Gelsinger was an eighteen-year-male with ornithine transcarbamylase (OT) deficiency, a genetic disease in which the individual lacks a functional copy of a gene that codes for OT, which plays an important role in protein metabolism. Most children born with this condition die in infancy, but Gelsinger had a mild form of the illness which had been well-managed through with drugs to help him metabolize proteins and dietary restrictions. Gelsinger enrolled in a Phase I (first in human) gene therapy trial at the University of Pennsylvania. The goal of the study was to determine whether it was possible to use an adenovirus vector to transfer copies of the OT gene into the subject's liver. The investigators had planned to perform the experiments on children with the disease but decided to focus on adults, based on the advice of bioethicist Art Caplan, who argued that parents might face self-imposed emotional pressures to consent for the experiment. Although the study had a small chance of benefiting Gelsinger, its main purpose was to demonstrate whether the procedure would work and be safe. Unfortunately, Gelsinger developed a severe immune response to the infusion of the adenovirus and died shortly thereafter as a result of participating in the study (Resnik 2007a). Gelsinger's family sued the study's principal investigator, James Wilson, Caplan (who was later dropped from the lawsuit), the university, and Genovo, the company which sponsored the study. The lawsuit, which was settled of our court, alleged that the investigators mislead Gelsinger about the benefits and risks of the study and had failed to inform him about adverse effects (including death) in prior animal experiments, and the investigator's and university's financial interests. Wilson had 20 patents on gene therapy techniques, some of which had been transferred to the university. Wilson also helped to start Genovo and held 30% of its stock even though

[16] See Chap. 10 for further discussion of COIs.

university policies required that equity interests be 5% or less. The university also owned stock in Genovo.

The FDA and OHRP investigated the incident and found that there were problems with adverse event reporting in gene therapy research and that the consent document that Gelsinger signed was inadequate. The NIH and Association of American Medical Colleges revised their COI guidelines for research with human subjects in response to this episode. Gelsinger's death undermined the public's trust in gene therapy research and set the field back several years (Resnik 2007a; Gelsinger and Shamoo 2008). In an editorial commenting on the incident, DHHS Secretary Donna Shalala observed that "Unfortunately, the public's confidence in our work, our competence, and our ethics has been seriously shaken (Shalala 2000:8)." Attorney Alan Milstein, who represented the Gelsinger family, now specializes in bioethics and clinical trials litigation (Sherman Silverstein 2017). Jesse Gelsinger's father, Paul Gelsinger, had this to say about the COIs in this case:

> The financial conflicts of interest for both the sponsor (James Wilson) and the University were basically ignored by the University's Conflict of Interest Committee. This led to a blindness on the part of all parties to the dangers they were seeing. These were not bad men doing evil. They were men blinded by ambition and greed. They have told me that they could not have foreseen Jesse's death, yet their data was screaming at them to stop. We trusted a system that was untrustworthy, one that didn't even pay attention to its own stops…So, my son, doing the right thing, was killed by a system and people rife with conflicts of interest, and real justice has been found to be very lax. It's essentially business as usual (Gelsinger 2008).

In June 2001, not long after the Gelsinger incident, another significant death of a human research subject occurred when Ellen Roche, a healthy 24-year-old technician at Johns Hopkins University (JHU), died from respiratory failure a month after inhaling hexamethonium as part of study to better understand the causes of asthma. In July of that year OHRP temporarily halted most of JHU's federally-funded human subjects research. An investigation into the incident found that study investigators had not adequately reviewed the literature on the risks of inhaling the drug. Most of the participants in the experiment were JHU employees (Keiger and De Pasquale 2002).

2.9 Concerns About Research on Human Biosamples

During the 1990s, there were growing ethical concerns about research involving human biosamples (e.g. blood, tissues, DNA). Biosamples are playing an increasingly important role in biomedical research. Scientists can use biosamples to understand basic physiologic and metabolic processes and mechanisms, as well as relationships between genetics, environment, and disease, and clinical investigators can use them to measure the effects of medical treatments. Many biomedical researchers collect and store human biosamples for their own work or to share with other scientists. Some studies involve the development of biobanks which store

biosamples and associated clinical or genetic data. There are many different types of biobanks ranging in size from a few hundred samples to millions of samples. Some are non-profit organizations operated by academic institutions or government agencies, while others are for-profit organizations run by private companies. Some have governing boards, while others do not (Weir and Olick 2004; Budimir et al. 2011).

Most researchers today obtain informed consent from human subjects before collecting biosamples from them. In thinking about the ethics of biosamples, it is useful to distinguish between three types of samples:

> Personally identified samples: the samples include the subject's name, medical record number, address, or other information that can personally identify him or her;
>
> De-identified samples: the investigator has removed personally identifying information from the samples but marked them with a code linked to personally identifying information;
>
> Anonymous samples: the samples include no identifying information; if the samples were coded, the key to the code has been destroyed.

The Common Rule does not require consent from the human subject when researchers are using anonymous biosamples left over from medical procedures, or de-identified biosamples collected by another researcher who has obtained the subject's permission to use and share the samples (Weir and Olick 2004; Shamoo and Resnik 2015).

Leftover tissues and blood from medical procedures have long been an important resource for researchers. Before the 1990s, doctors rarely obtained their patients' consent to use leftover blood or tissues for research.[17] In 1990, the California Supreme Court decided a case with implications for this practice. In 1976, John Moore had a splenectomy at the University of California at Los Angeles (UCLA) medical center to treat his leukemia. David Golde, the physician who had recommended the surgery, discovered that Moore's tumor was overproducing proteins that regulate immune cell functions known as lymphokines. Golde decided to develop a cell line from Moore's tissue and asked him to make several additional visits to the medical center to provide blood and tissue samples, without telling him the true purpose of the visits. Golde reached an agreement with UCLA and a pharmaceutical company to commercialize the cell line. Golde patented the cell line and transferred it to UCLA, which sold the patent to company. The cell line generated several billion dollars in revenue (Resnik 2007a). Moore eventually found out about this clandestine affair and sued the university, the company, and the investigator for conversion (wrongfully taking or using someone's property) and lack of informed consent. The court did not recognize Moore's conversion claim because it said that he did not have a property interest in tissue which he had abandoned, but it did recognize his informed consent claim because it said that Golde should have told Moore about his true reasons for collecting the additional samples and his plans to commercialize the cell line (Moore v. Regents of the University of California 1990). Several courts have revisited the property issues addressed in this case, but so far

[17] See also discussion of the Lacks case in Chap. 1.

none have recognized that patients or human subjects have property rights pertaining to tissues that they have abandoned or voluntarily given away (Shamoo and Resnik 2015).

Consent for use of data was an important issue in 1998 when Iceland's government created a database of the health care records of its citizens which could be linked to genealogical and genetic data. The government granted an exclusive license to deCODE genetics, a for-profit company, to create and manage the database. Only de-identified data would be shared with biomedical researchers. The database was controversial because it used an opt-out consent process: citizens' records would be included in the database unless they requested to not include their data. Critics argued that an opt-out process did not grant sufficient respect for citizens' rights to control access to their medical records, because some people might not know about the opt-out procedure or understand how to opt-out (Weir and Olick 2004).

Consent for the use of samples and data was also an important concern in a dispute between Arizona State University (ASU) and the Havasupai Native American tribe, which unfolded in the early 2000s. In 1990, ASU investigators collected 200 blood samples from members of the tribe for a study they told tribal leaders would focus on the genetics of diabetes. However, the consent form indicated that samples and data would also be used from research on mental illness. Members of the tribe became upset when they learned that researchers had shared samples and data with other scientists without their permission and used them to study schizophrenia, tribal in-breeding, and the tribe's evolutionary history. They filed a $50 million dollar lawsuit against the university and the investigators, which was settled out-of-court in April 2010. Under the terms of the settlement, ASU agreed to return the blood samples to the tribe and pay the 41 study participants $17,000 each. This incident soured the university's relationship with the tribe and many members vowed to never participate in ASU studies again (Mello and Wolf 2010). In her testimony before the President's Commission for the Study of Bioethical Issues, Havasupai Tribal Council member Carletta Tilousi said: "The reason why I'm here today was a lot of our blood samples were misused. The people's trust in the institution was shattered (Tilousi 2011)."

Consent for access to blood samples was also an issue in a U.S. law passed on December 14, 2014, which required investigators to obtain parental consent to conduct research on de-identified blood samples from newborn screening programs (Bayefsky et al. 2015). All states have mandatory newborn screening programs supported by funds from the state and the Health Resources and Services Administration, a federal agency. States test for a varietal of congenital diseases and disorders including deafness, cystic fibrosis, phenylketonuria, sickle cell anemia, and severe combined immune deficiency (National Newborn Screening and Global Resource Center 2014). Prior to the enactment of the law, parental consent was not necessary to conduct research on de-identified leftover newborn blood samples, because this would not be classified as human subjects research under the Common Rule. The new law defined research on de-identified newborn blood samples as human subjects

research, so consent would be required (Bayefsky et al. 2015).[18] Some investigators objected to this change in federal policy because would impede research, since many parents might refuse to consent. They also argued that consent should not be necessary because research on de-identified blood samples poses virtually no risk to newborns (Bayefsky et al. 2015).

Research involving the analysis of biological samples or data poses no physical risks to the subjects, other than the small risks associated with sample collection, such as bleeding or bruising from a venipuncture. The other main risk is the potential loss of confidentiality if personal information is inadvertently disclosed, but this risk can be minimized by implementing security measures, such as removing personal identifiers from the samples or data, limiting access to samples or data, encrypting data, and keeping samples in a secure place (Shamoo and Resnik 2015). If research on biological samples or data is low risk, why have people raised ethical concerns about it?

One reason is that some people would like to control how their biological samples or data are used. In the ASU case, members of the Havasupai tribe did not want their samples or data to be used from research on mental illness, in-breeding in the tribe, or tribal origins. Some people may object to having their biological samples or data used for commercial purposes. Women who donate eggs for research may not want researchers to use them for cloning human embryos or creating human-animal chimeras (Shamoo and Resnik 2015).

Another reason is that de-identification may no longer guarantee confidentiality because statisticians have developed methods for re-identifying individuals in de-identified genomic databases from a sample of their DNA or their phenotypic information, such as medical diagnoses, height, weight, gender, and so on (Lowrance and Collins 2007, Homer et al. 2008). Statisticians have also shown how to identify individuals in de-identified databases based on their some of their demographic and medical information (see discussion in Chap. 6).

The NIH revised its genomic data-sharing policy in 2010 due to concerns about re-identification. Previously, the NIH had required funded investigators to make their human genomic data available to the public by depositing it one of two publicly accessible NIH websites, the Genetic Markers of Susceptibility database or the database of Genotypes and Phenotypes. Under the new policy, most of the human genomic data on these websites will be accessible only by means of data use agreements in which recipients promise not to share data with others without permission or attempt to re-identify individuals. Some limited human genomic data is still accessible without a data use agreement (Resnik 2010a).

Another concern with biosamples that emerged was sharing individualized results of laboratory tests or procedures with research subjects (Resnik 2011a).[19] Investigators often collect information likely to be useful to research subjects, such

[18] This change was consistent with a proposed revision to the Common Rule, which would define all research on human biological samples as human subjects research (Department of Homeland Security et al. 2015). Common Rule revisions will be discussed in more depth in Chap. 11.

[19] These issues are discussed in more depth in Chap. 5.

as pulse, blood pressure, blood sugar levels, body mass index, and so on. Subjects may want to share this information with their physicians or retain it for their own records. If subjects have abnormal test results, investigators may recommend that they consult a physician or seek immediate medical attention, depending on the urgency of the problem. In 2001, the Maryland Supreme Court ruled that investigators have legal duties to inform research subjects about significant health risks discovered during the course of a study (Grimes v. Kennedy Krieger Institute, Inc. 2001). The litigation in this case pertained to an EPA-funded study on lead abatement methods conducted by the Kennedy Krieger Institute, a research center associated with JHU, in the 1990s. The aim of the study was to determine whether less expensive forms of lead abatement are as effective at preventing exposure to lead as full lead abatement, which could cost as much as $10,000 per home. The study enrolled 25 Baltimore, MD families with small children living in the home. Twenty families living in homes with lead paint were randomly assigned to groups receiving the full level of lead abatement, or $1650, $3500, or $6000–$7000 worth a lead abatement. The study also included a control group of five families living in homes without lead paint. Investigators measured lead levels in children's blood and in dust, soil, and waters samples from the homes. They told the families that they would inform them of dangerous lead levels in their children's blood or in the home. Two families sued the investigators and KKI on the grounds that the investigators had acted negligently by not informing them of dangerous lead levels in a timely fashion. The investigators did not inform Viola Hughes that her daughter, Erica Grimes, had dangerous lead levels in her blood until 9 months after they had detected this hazard. The defendants made a motion to dismiss the case on the grounds that they did not have a legal duty to inform the research subjects of dangerous lead levels. However, the court ruled in favor of the plaintiffs. The court found that the investigators have legal duties to the participants based on a special relationship implied by the federal research regulations and the contractual obligations in the informed consent document (Grimes v. Kennedy Krieger Institute, Inc. 2001). Although other court cases had addressed clinical investigators' legal obligations to research subjects, this was the first case in which a court found that investigators had legal obligations to research subjects who are not their patients.

2.10 Conclusion: Human Research Regulations and Guidelines in Historical Context

For much of the history of science and medicine, society has entrusted investigators with protecting the rights and welfare of human research subjects. The protection of human subjects depended, in large part, on the integrity of the investigators (Moreno 2001). While investigator integrity is still a vital part of research, in the 1970s protection of human subjects shifted toward external oversight by means of regulations and guidelines. These legal rules and ethical standards emerged as a reaction to

Fig. 2.8 Jesse Gelsinger (age 18) with Rocky Balboa statue (Used with permission from Paul Gelsinger)

egregious abuses of human subjects and have continued to evolve since then (Moreno 2001; Marshall 2002; Wertheimer 2011). As incidents have come to the public's attention, government officials, scientists, bioethicists, and policymakers have taken steps to restore and maintain the public's trust. This chapter has catalogued some of the events and trends which have alarmed the public, such as: The Nazi experiments, the Tuskegee study, the Willowbrook hepatitis experiments, the secret human radiation experiments, the CIA's mind control research, the deaths of Jesse Gelsinger and Ellen Roche, the Havasupai case, the CHEERS study, and reports of fraud, bias, and COI in biomedical research. Each step of the way, the trend has been to adopt new regulations and guidelines or revise existing ones to protect the rights and welfare of human subjects in research (Mastroianni and Kahn 2001; Marshall 2002; Rhodes 2005) (Fig. 2.8).

The result of this shift toward external oversight is that research with human subjects is one of the most heavily regulated—and some would say overregulated—social activities in the U.S. (Schneider 2015). Despite the presence of numerous legal rules and ethical standards pertaining to research with human subjects, controversies and scandals still arise. Controversies continue to emerge despite ample regulation and guidance because research with human subjects involves ethical conflicts between the rights and welfare of the individual and the goal of advancing scientific knowledge that can benefit society. Regulations and guidelines, by themselves, cannot resolve these tensions because issues can reemerge when interpreting, applying, and prioritizing rules.

If we assume that there is sufficient proof to support the historical/sociological thesis that the regulations and guidelines have evolved to restore and maintain public trust in research is correct, the ethical/philosophical question one needs to ask is whether these rules are an appropriate reaction to a crisis of confidence. Some authors, such as Rhodes (2005), Schrag (2010), Wertheimer (2011), Sachs (2011), and Schneider (2015) argue that some of these regulations and guidelines have gone too far and impede valuable research. One of the main reasons why federal agencies have revised their regulations is to reduce regulatory burden on researchers (Emanuel and Menikoff 2011). Several writers have observed that human research subjects have more protections than most people have outside of the research context (Edwards et al. 2004; Rhodes 2005; Miller and Wertheimer 2007; Wilson and Hunter 2010; Resnik 2015a). For example:

- The regulations allow healthy adults to take risks in research only if an IRB determines that the risks are reasonable in relation to the expected benefits. Outside of the research context, healthy adults are free to make their own decisions concerning risks and are free to perform many risky activities, such skydiving, mountain climbing, smoking tobacco (and marijuana in some states), riding motorcycles, and so on (see discussion or risks in Chap. 7).
- The regulations allow human subjects to withdraw from a study at any time without penalty. Outside of the research context, a person may incur a penalty for breaching a contract.
- The regulations include numerous types of information that must be conveyed to the subject (or his or her representative) and documented for consent to be valid. Outside of the research context, people are free to decide what to include in a contract if they reach some agreement on what each party will do under the contact.
- The regulations prohibit human subjects from waiving or appearing to waive legal rights during consent. Outside of the research context, people are free to waive various kinds of legal rights. For example, one could agree not to sue a skydiving company as a condition of using its services.
- The regulations place limits on the risks that children, pregnant women, and prisoners may be exposed to in research that does not provide direct benefits. Outside of the research context, parents are free to expose their children to various risks beyond what would be allowed by the regulations. For example, parents can allow their children to participate in contact sports, ride horses, work on farms, scuba dive, and so on. Pregnant women are free to ride horses, smoke, drink alcohol, and so on. Prisoners are routinely exposed to far greater risks than they would be allowed to face in non-beneficial research (see discussion in Chap. 9).
- Outside of the research context, we usually do not place any limits on the amount of money that someone may be paid to perform a job. Although the research regulations do not place any limits on the amount of money that researchers can offer subjects for their participation, many bioethicists have argued that offering

people too much money can be unethical because it may coerce or induce their participation (see Grady 2001 and discussion in Chap. 5).

Miller and Wertheimer (2007) have labelled these additional protections "paternalism" because they involve controlling people's decision-making for their own good. Miller and Wertheimer follow the standard philosophical literature (see, for example, Dworkin 2014) in distinguishing between hard and soft paternalism. Hard paternalism involves restricting the actions or decisions of a person who is fully autonomous (e.g. a competent adult) for their own good, whereas soft paternalism involves restricting the actions or decisions of someone who is not fully autonomous (e.g. a child or mentally disabled adult). A law requiring all automobile passengers, including adults, to wear seatbelts is an example of hard paternalism, whereas a law requiring children to wear helmets when bicycling is an example of soft paternalism. Most people would accept some form of soft paternalism because they agree that people who have compromised decision-making or lack information deserve some protection from harm. In a famous example, nineteenth century British philosopher John Stuart Mill (1806–1873), an ardent defender of liberty, conceded that it would be acceptable to stop a competent adult from crossing a dangerous bridge if he or she doesn't know the bridge is dangerous and there is no time to warn him or her. Mill also argued that it is acceptable to restrict the liberty of mentally disabled people for their own good (Mill 1978).

Hard paternalism is generally more controversial than soft because most people value personal freedom and do not want outside interference in their decisions or actions. People would like to make their own choices, even choices which many would consider to be too risky or ill-advised. While the additional protections for children, neonates, fetuses, and prisoners and mentally ill people could be viewed as soft paternalism, most of the additional protections for competent adults would be hard paternalism (Miller and Wertheimer 2007). For example, limiting the amount of money that competent adults can receive for research participation to prevent them from making decisions against their better judgment would be hard paternalism.

Soft paternalism can also be controversial if it provides too much protection for people with compromised autonomy. For example, each year in the U.S. about 400 children and adolescents under the age of 20 are killed while riding bicycles and about 250,000 are seriously injured (Centers for Disease Control and Prevention 2011). Suppose the U.S. enacted a law that prohibits anyone under the age of 18 from riding a bicycle. Parents would probably object to such a law on the grounds that bicycle riding offers important benefits to their children, such as exercise, entertainment, and transportation, and that they should be allowed to decide whether these benefits outweigh the risks.

Although I consider paternalism to be an important issue in research with human subjects, I prefer to frame the issues in terms of questions concerning protectionism, i.e. what justifies a decision or policy that protects the rights or welfare of human research subjects? It may seem to some readers that the difference between paternalism and protectionism is a terminological issue of little consequence. However,

I think it is important to make this distinction because protectionism goes beyond mere paternalism, which focuses on the external control of an individual's actions or choices for their own good (Dworkin 2014). Protectionism could include policies that promote the welfare of individuals without directly controlling their decision-making. For example, requiring a clinical trial to have an independent data and safety monitoring committee would be protectionistic but not paternalistic. Likewise, providing medications to human subjects in a clinical trial in a developing country after the trial ends would be protectionistic but not paternalistic. Paternalism is a type of protectionism.

Another reason why I prefer to focus on protectionism rather than paternalism is that paternalism can be difficult to distinguish from other doctrines, such as the public harm principle or the public welfare principle, when it comes to social policy (Feinberg 1986). For example, consider a law that prohibits gambling. On the one hand, it could be viewed as a form of strong paternalism because it controls the choices of competent adults for their own good. On the other hand, it could be justified on the grounds that it protects society from the harmful effects of gambling, such as gambling addiction, and the organized crime often associated with gambling.

Deciding whether an action or policy pertaining to research with human subjects is overprotective or not protective enough requires one to balance the competing values or principles at stake, i.e. the rights or welfare of the research subjects and the need to advance human knowledge to benefit society. As we have seen, difficult choices continue to arise in research with human subjects, despite increasing regulatory oversight. To decide how to balance competing values or principles, we need a decision-making framework we can use to establish priorities related to policy development and decision-making. Moral theories offer such a potential framework. Could moral theories provide us with some useful guidance for answering questions concerning the ethical issues in research with human subjects? The next chapter will address this question.

Chapter 3
Moral Theory

In the previous chapter I argued that a review of the history of the ethics of research with human subjects indicates that the regulations and ethical guidelines have evolved in response to egregious abuses of human subjects and ethically questionable research. Society has adopted rules to prevent these problems from occurring again and to restore and maintain public trust in research. The regulations and guidelines form a system of rules designed to protect the rights and welfare of human research subjects. Ethical dilemmas involving research with human subjects continue to emerge, however, because the rules do not completely resolve fundamental questions related to the conflict between the rights and welfare of human subjects and the goal of advancing human knowledge to benefit society. To be sure, regulations and guidelines can help investigators, IRBs, institutional leaders, policymakers, and concerned citizens address these issues, but questions remain because dilemmas occur when interpreting, applying, prioritizing, and revising regulations and guidelines. What is needed, I argued, is an ethical decision-making framework which justifies rules and policies and can establish priorities when ethical conflicts arise. This chapter will consider whether moral theories can provide such a framework.

3.1 What Is a Moral Theory?

A moral theory is a set of statements used to systematize and codify our judgments concerning standards of conduct or behavior (Timmons 2002). Moral theories provide us with an account of what we should do (i.e. duties or obligations), what is good or worthy of pursuit (i.e. moral values), what is fair or just, and how we should our lives (i.e. virtue). Moral theories usually include general principles for making decisions in particular cases as well as definitions of morally relevant concepts. For example, Christian ethics includes a number a moral principles, such as the Golden Rule ("do unto others as you would have them do unto you") and the duty to love

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one's neighbor. German philosopher Immanuel Kant's (1724–1804) moral theory (discussed below) includes definitions of dignity, autonomy, categorical imperatives, hypothetical imperatives, and good will (Timmons 2002).

Moral theories differ from scientific ones because we cannot confirm a moral theory by means of observations, tests, or experiments (Harman 1977). Physicists and astronomers tested Einstein's general theory of relativity, for example, by attempting to observe whether massive objects (such as stars or galaxies) can bend light. The theory was confirmed, in part, because it correctly predicted that we should be able to observe this phenomenon (Dyson et al. 1920). We cannot perform similar types of procedures for moral theories, however (Harman 1977). For example, if you observe someone torturing a cat, you may form the judgment that this is wrong, but the judgment is not based on directly observing some quality of wrongness in this act in the same way that you could observe the cat's weight, sex, eye color, or other physical, chemical, or biological properties (Harman 1977).

It may be objected, however, that we indirectly observe many physical, chemical, or biological properties and objects, so that we should also be able to indirectly observe moral properties. For example, we can use microscopes to observe cells and we can infer deoxyribonucleic acid (DNA) sequences from chemical analyses. Scientists who indirectly observe properties or objects rely on theories to tell them how to make these observations. For example, theories of light inform scientists how to use a microscope to observe microscopic objects, and chemical theories inform scientists how to infer DNA sequences from chemical reactions. One might argue we can rely on moral theories to indirectly observe moral properties (Harman 1977). We can use moral theories and concepts and emotional reactions to form moral judgments about the acts, events, or states of affairs we observe (Greene 2013). For example, someone who observes a cat being tortured and concludes that this act is immoral might be relying on a background moral theory which tells him or her that it is wrong to inflict pain on animals needlessly.

This objection does not show that we can confirm moral theories by means of observations or tests because the indirect observations of physical, chemical, or biological properties or objects we make by means of scientific instruments, experiments, or tests are more robust than the "observations" of moral properties we may make based on our moral concepts and emotional reactions. First, physical, chemical, and biological observations, tests, and experiments are repeatable: different scientists, working in different laboratories, can analyze a piece of DNA and report the same sequence data. Observations of cells, atomic structures, electrons, distant galaxies, and so on are also repeatable (Hacking 1983). Although many moral judgments are repeatable, many are not. Indeed, moral disagreement is pervasive (Timmons 2002). For example, scientists and ethicists strongly disagreed about the ethicality of the HIV prevention trials and the SUPPORT study discussed in Chap. 1.

Second, scientists can use different instruments, experiments, or tests to indirectly observe the same property or object. For example, biologists can observe the structure of DNA using x-ray crystallography techniques or an electron microscope (Hacking 1983). Though sometimes different moral theories will lead us to make the same moral judgments, often they do not. As we shall see below, different moral theories sometimes imply radically different moral evaluations of the same act, event, or state of affairs.

Third, often scientists can experimentally manipulate properties or objects which they indirectly observe to produce physical, chemical, or biological effects (Hacking 1983). For example, physicists can manipulate materials at the nanoscale to make wires which carry electric current. Molecular biologists can splice DNA into plant genomes to produce useful traits, such as drought-tolerance. We cannot make similar sorts of experimental manipulations of moral properties, because moral properties do not produce physical, chemical, or biological effects. In ethics, we can manipulate hypothetical scenarios (such as the trolley problem, discussed below) to produce different moral judgments, but these effects are merely psychological.

If we cannot confirm moral theories by means of observations, experiments, or tests, how can we prove or disprove them? Many philosophers accept Johns Rawls' (1921–2002) idea that we can justify moral theories by means of a method known as reflective equilibrium (Rawls 1971). To follow the method, one begins with considered judgments (or intuitions) of right/wrong, good/bad and so on, in particular cases. One then forms general principles (or theories) to systematize those judgments and tests those principles against the original judgments and new ones. One may revise one's principles to accommodate those judgments, or one may reject some judgments, based on one's principles. As the process continues, one eventually reaches a point (known as reflective equilibrium) in which moral principles and judgments cohere (Rawls 1971).

Some philosophers have argued that Rawlsian reflective equilibrium should be expanded to include scientific facts and highly confirmed theories, so that moral theory will be consistent with the findings of modern science (Daniels 1996; Sayre-McCord 1996; Tramel 2015). This expansion of reflective equilibrium is known as wide reflective equilibrium (See Fig. 3.1). Requiring that moral theories be consistent with the findings of modern science does not imply that morality is based on or derived from science; it only means that morality should not make claims which science has proven to be incorrect. For example, modern science has discredited the racist idea that some races are intellectually and morally inferior (Fish 2015). Racism should not be assumed by or implied by any moral theory.

One of the potential shortcomings of reflective equilibrium is that the moral judgments used in the method are susceptible to cultural, social, religious, political, or economic biases (Rawls 1971; Daniels 1996). For example, most whites living in

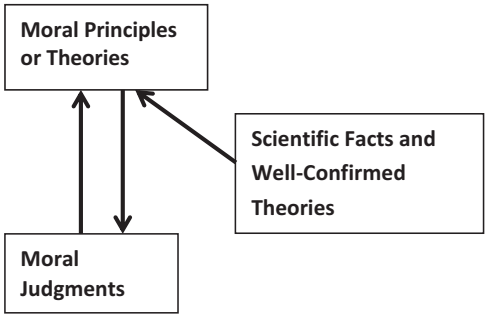

Fig. 3.1 Wide reflective equilibrium

the Confederate states during America's Civil War would have accepted the moral judgment that enslaving blacks is ethical, and any moral theory they adopted would have been impacted by this bias. According to proponents of the reflective equilibrium, biases can be overcome, in the long run, by repeatedly revising moral principles or theories in response to scientific findings and moral new judgments. To counteract the biases inherent in "commonsense" morality, one should caste a wide net and be open to new moral judgments and revisionary moral ideas (Greene 2013). For example, white southerners living in the Confederate states during the Civil War could counteract their cultural biases by being open to the idea that blacks have the same moral standing as whites. Thus, moral principles and judgments in reflective equilibrium should represent a broad moral consensus, rather than the judgments or views of particular cultures, societies, or historical periods.

While this response to the possibility of bias seems plausible, it creates a problem: if reflective equilibrium is reached in the long run, then how should we act in the short run? We must make moral decisions in the present moment and cannot wait for reflective equilibrium to provide us with the "correct" moral theory. How can we be assured that the decisions we make in the short run are not biased? While this is indeed an important problem, it is not unique to reflective equilibrium, since all moral theories must confront this issue. The most prudent course of action that one can take is to make the best decision possible, under the circumstances, realizing that one may need to revisit the decision in light of new scientific findings or moral judgments. When it comes to moral decision-making, we should accept that we are fallible and we should be prepared to correct mistaken ethical judgments.

Assuming the one accepts reflective equilibrium as a method for justifying moral theories, an important question still remains: what criteria should we use to decide whether to accept, reject, or modify a particular moral theory during the reflective process? According to Timmons (2002), moral theories should be evaluated in terms of their ability to perform two fundamental tasks. The first is that they should provide us with a workable procedure for deciding right/wrong, good/bad, on so on, in particular cases. A moral theory should have practical applicability. The second is that a theory should offer a cogent explanation of morality, i.e. what makes something right or wrong, good or bad, and so on. To provide a cogent explanation of our morality a moral theory should: a) be logically consistent; b) be consistent with scientific facts; c) make sense of our intuitive moral judgments; d) and enhance our understanding of our morality. I shall refer to these goals and criteria when evaluating moral theories.

I will now consider some moral theories with an eye toward how they would approach the basic ethical dilemma in research with human subjects, i.e. the interests/rights of the individual vs. society. In the interests of time, I will focus on some of the most influential moral theories.

3.2 Moral Subjectivism and Relativism

I will begin my survey by examining moral subjectivism and relativism, since if either of these views is correct, it may not be possible to develop a workable framework for addressing ethical dilemmas in research with human subjects, because accepting either theory would undermine any effort to develop international ethics guidance. Since I am optimistic about the prospect of developing an ethical framework that applies globally, I need to address moral subjectivism and relativism before evaluating other theories.

Moral subjectivism is the view that what is right/wrong, good/bad is relative to a particular person: there is no difference between what a person believes is morally correct and what is morally correct. If I believe that it is morally acceptable for me to abuse animals, harm people, lie, cheat, steal, etc., then it is morally acceptable for me. Morality has to do with matters of taste, personal preferences, or subjective attitudes and opinions (Ayer 1952).

Subjectivists have developed several arguments for their position. According to the first argument, we should regard morality as subjective because we cannot prove or disprove moral statements by means of observations, tests or experiments (Ayer 1952). However, as argued above, we can test moral statements by non-empirical methods, such as reflective equilibrium. These non-empirical methods allow us to reach agreement on moral principles, even if they do not constitute empirical evidence for ethical theories. This brings us to the subjectivist's second argument: we should accept subjectivism because we cannot reach agreement on moral issues.

However, there is strong evidence that we can reach agreement on many moral topics even if we still disagree about others. Most people will agree that it is wrong to kill people, abuse animals, lie, cheat, steal, etc. (Barcalow 1994; Pojman 2005).

According to the third argument, morality is subjective because moral statements are not capable of being true or false. Moral statements express emotions, feelings, or attitudes, but they do not express facts with truth-values (Ayer 1952). The response to this argument is complex, but one can respond to this argument by asserting that what matters in morality is not whether moral statements are true or false but whether they can be appropriately justified. Most people will agree that the statement "murder is wrong" is justified (Sayre-McCord 1996; Tramel 2015). If we agree that a moral statement is justified, then we can use it to guide conduct and make moral decisions.

Moral relativism is the view that what is right/wrong or good/bad is relative to a particular or culture: there are no moral standards which transcend particular cultures. "When in Rome, do as the Romans do" is the motto of this theory. Although philosophers have discussed moral relativism since ancient times, the theory increased in popularity during the twentieth century due to anthropological research on variations in social norms and taboos across different cultures (Barcalow 1994; Benedict 1946). The argument can be stated as follows:

1. Different cultures have different views concerning what is morally right and wrong, good and bad, and so on.

2. If cultures have different views about a particular topic, then the correct view of the topic is relative to that culture; there is no correct view on the topic independent of a culture.
3. What is morally right/wrong, good/bad, etc. is relative to a culture.

Let's consider whether this is argument is sound. The first premise is based on anthropological observations of cross-cultural differences in moral beliefs and norms. There is substantial evidence that different cultures have differing views on homosexuality, the status of women, capital punishment, children's rights, and many other moral issues. However, there is also evidence that cultures share some common moral beliefs and norms (Macklin 1999; Pojman 2005). For example, most cultures regard murder, battery, rape, theft, fraud, cheating, incest, and adultery as morally wrong. There is also considerable evidence from psychology that people from different cultures form similar moral judgments in response to decision-scenarios, and that the parts of the brain involved in moral judgment are the same throughout the human species (Greene 2013). Sociobiologists argue that evolutionary biology provides an explanation for cross-cultural similarities in moral norms, because morality has evolved as an adaptation that promotes cooperation within a social group (de Waal 2009). Thus, this empirical premise in the argument is only partly true. At the very least, it should be restated more precisely.

The second premise claims that if cultures disagree about a topic, then there is no correct view on the matter independent of society/culture. But why should we accept this premise? If culture A believes that the Earth is flat and culture B believes it is round, should we conclude that there is no correct view of the matter independent of these cultures? People from different cultures and societies have disagreed (and continue to disagree) about medicine, astronomy, biology, geology, and many other topics, yet we do not conclude that the correct view on those topics depends on what culture or society you are in.

A defender of relativism might reply that the question of whether the Earth is flat or round is an empirical issue which can be settled by means of observations, tests, and experiments. Likewise, medicine, astronomy, geology, biology, and so on also deal with empirical questions. Scientists from different cultures can rely on evidence from observations, tests, and experiments to reach agreement on empirical questions, even if members of those cultures disagree about these questions. Moral questions are not empirical, however (Harman 1977). Hence, the relativist would assert that cross-cultural disagreement concerning moral questions demonstrates that there are no culturally-independent, correct views on these questions.

While the relativist makes an important point, the reply does not justify the conclusion that morality is relative to culture because it may be possible for people from different cultures to agree on moral issues through cross-cultural discussion and debate (Pojman 2005). People from different countries have come together many times throughout history to reach consensus on moral topics, such as human rights, slavery, human trafficking, and torture. For example, in 1948 over 50 members of the United Nations drafted a Universal Declaration of Human Rights (United Nations 1948). In 1975, over 80 members of the United Nations drafted a convention against torture (United Nations 1975). As discussed in Chap. 2, nations around the world condemned

the Nazi experiments on concentration camp prisoners, and the Nuremberg Code reflects an international consensus on the ethics of research with human subjects. Other international codes, such as the Helsinki Declaration, reflect a similar consensus.

Another problem with the argument for moral relativism is that 'culture' is not clearly defined. Is culture defined by a geographic region, such as nation, state, or city? Can culture be equated with race, ethnicity, religious affiliation, political allegiance, profession, or occupation? The degree of cultural variation in moral beliefs and norms may vary depending on the definition of 'culture' one uses. Without a clear definition of 'culture,' the argument for moral relativism commits the fallacy of ambiguity because 'culture' may mean different things in the premises and conclusion (Macklin 1999; Timmons 2002).

Some people may subscribe to moral relativism because they believe we should not judge or interfere with other cultures, and they believe that acceptance of relativism justifies tolerance. However, the connection between relativism and tolerance is not straightforward, since some cultures may practice intolerance toward other cultures. Suppose the culture A is very peaceful and tolerant toward other cultures but culture B is very aggressive and intolerant. The relativist cannot say which culture has the correct view, because the relativist holds that what is right/wrong depends on what culture you are in. This is a very limited justification of tolerance. To provide a general defense of tolerance, one would need to appeal to moral principles that transcend any particular culture, which the relativist cannot do (Timmons 2002).

While tolerance is an important virtue, morality sometimes requires us to take a stand against actions or behaviors which are clearly wrong. For example, I think most people would agree that what the Nazis did to the Jews before and during World War II was morally abominable. We would also have similar reactions to the Hutu-led government's slaughter of nearly one million Tutsis during the Rwandan civil war, and mass-killings of Christians and Muslims conducted by the Islamic State of Iraq and Levant. Tolerance does not require us to sit by idly when evil occurs; we should condemn it and take action against it if necessary (Macklin 1999).

The relativist's condemnation of moral evil is very limited and weak, however. A relativist could say what the Nazis did to the Jews was wrong according to the cultural standards of the Jewish people, but that it was acceptable within Nazi culture, or perhaps the broader German culture. This type of view flies in the face of commonsense, since most people would agree that what the Nazis did was wrong without any qualifications: it was wrong not just from the perspective of Jewish culture but from any reasonable perspective.

In addition to the aforementioned problems, moral relativism appears to be incompatible with intra-cultural criticism and reform. Throughout U.S. history, moral visionaries have criticized practices that many people regarded as acceptable and have inspired changes in attitudes, beliefs, practices, and laws. For example, leaders of the Civil Rights Movement criticized racial segregation and discrimination and helped to move the U.S. in the direction of racial equality. These visionaries appealed to moral ideals which transcend the ethical norms found in popular culture. If moral relativism were correct, then intra-cultural criticism and reform would be conceptually incoherent, since there are no moral ideals beyond what is contained within one's culture. But most of us would agree that intra-cultural criticism

and reform is conceptually coherent and that moral visionaries have brought about important changes in the U.S. and many other countries. Moral relativism has no cogent explanation of this phenomenon.

While I believe that relativism is not a tenable philosophical position, I think that it raises important issues concerning cultural variation that moral theories should address in some fashion. It might be the case that differently cultures interpret and apply common ethical standards differently (Macklin 1999). For example, in some Islamic cultures a woman is not allowed to consent for medical treatment by herself but must have the consent of her husband (if married) or an older male relative (Afifi 2007). If we assume that informed consent is a universal moral norm, should we view this Islamic practice as a violation of the norm or an as acceptable variation of a moral norm? Does it make sense to say that informed consent can mean different things in different cultures or nations? At what point would we not consider a cultural practice to involve consent at all? We will take up these sorts of questions again in Chaps. 4 and 5. Other chapters will also address the topic of cultural variations in research ethics.

3.3 Classifying Moral Theories

If we accept the idea that it is possible to develop a moral theory that applies to different individuals, cultures, communities, societies, and nations, we need to ask what that theory should be founded upon. As we shall see below, different moral theories provide different foundations for morality: some base it on God's will; some on human nature; and some on pure reason.

Before we begin our examination of moral theories, it is importance to distinguish between two types of theories: teleological (or goal-directed) theories and deontological (or duty-based) theories. Teleological theories hold that morality consists in promoting things we regard as valuable, such as happiness, knowledge, virtue, or human life, whereas deontological theories hold that morality is concerned with obeying moral duties. Deontologists claim that whether an action is right or wrong depends on the nature of the act, and its relation to our duties or rights, rather than the goals served by the act (Timmons 2002). We shall now consider these different theories (See Table 3.1).

Table 3.1 Moral theories

Name of theory	Type of theory	Chief proponent
Divine command theory	Deontological	Various religions
Virtue ethics	Teleological	Aristotle
Natural law theory	Teleological	St. Thomas Aquinas
Utilitarianism	Teleological	John Stuart mill
Kantianism	Deontological	Immanuel Kant
Natural rights theory	Deontological	John Locke
Pluralism	Mixed	W.D. Ross

3.4 Divine Command Theory

The first moral theory we will consider is known as the divine command theory. This is the oldest moral theory, since it coincides with the advent of religion as a human cultural phenomenon. According to this theory, morality is founded upon God's will. Something is right/wrong because God commands it or would command it (Timmons 2002). All of the world's major religions—Judaism, Christianity, Islam, Buddhism, Hinduism, and African and Native American belief systems—include ethical principles and teachings. The divine command theory reflects how many people think about moral issues and understand their moral obligations, since many people look to their religion for moral guidance and inspiration. The divine command theory is usually construed as deontological, because it holds that morality consists in following God's commands. For example, the Ten Commandments are a set of rules that many Jews, Christians, and Muslims regard as morally obligatory. Despite its widespread influence, the divine command theory has some problems which prevent is from serving as a viable framework for thinking about the ethics of research involving human subjects.

The first objection to the theory was raised by the ancient Greek philosopher Plato (427–347 BCE) in the *Euthyphro* (Plato 2002). In this dialogue, Socrates asks Euthyphro whether something is pious (or moral) because it is loved by the Gods or is it loved by the Gods because it is pious. On the one hand, if something is moral because it is loved by the Gods, then this would imply that whatever the Gods love would be moral, even something which we would consider to be wrong. For example, suppose that the Gods commanded a man to kill his only son. Would this make it the right thing to do? Morality would seem to be arbitrary and possibly cruel or unjust if it depends on what the Gods love. On the other hand, if the Gods love what is moral because it is moral, then this would mean that morality is independent of what the Gods love. The Gods do not create morality but they are bound by it (Timmons 2002).

One way for the theist to deal with the *Euthyphro* problem is to concede that God does not create morality, but that He or She follows it perfectly. God's commands always conform to morality because God is perfectly good and omniscient. God understands and follows the moral law and apprehends what it the right thing to do in every situation. God would not command someone to do something wrong, because this would be against His nature (Timmons 2002). Of course, if morality exists independently of God, it should be also possible for human beings to access it, which raises the issue of why we would need God's mediation.

While proponents of the divine command theory may be able fend off the first objection, the second one presents greater difficulties. This objection addresses epistemological problems with the theory. Supposing that morality is based on God's will, how are we to know what is right or wrong, good or bad, and so on? There seem to be two choices: either moral knowledge comes from divine revelation (i.e. direct communication with God) or religious teachings. Divine revelation is a problematic source of moral knowledge because it is subjective and therefore

potentially erroneous. Suppose that a man says that God told him to kill his son. Should we believe that person or take steps to prevent him from committing murder? What if the man is mistaken and the divine revelation is really a voice he hears in his head as a result of mental illness? Divine revelation may be a useful source of inspiration for an individual, but it cannot be trusted for making decisions that impact the rights or welfare of others.

Religious diversity presents an intractable problem for someone who holds that moral knowledge comes from religious teachings. In addition to the major religious traditions mentioned above, there are also sects within those traditions, and practitioners within the same sect who have different interpretations of religious texts and doctrines. Some religions and sects have been at war with each other for thousands of years. Although most of these religions, sects, and interpretative frameworks agree on some common moral principles they also disagree on many topics, such as the morality of abortion, the death penalty, and homosexuality. How are we to decide which religion to follow for moral guidance? Moreover, how are atheists supposed to acquire moral knowledge? Can they only know what is morally right by embracing religion? We would seem to have very little hope of achieving any kind of consensus on moral issues if we hold that moral knowledge depends on religious teachings (Timmons 2002).

None of this need imply that religion is totally irrelevant to moral decision-making. People may still choose to rely on their religious views for personal guidance, motivation, and inspiration. Also, many religious and secular approaches to morality recognize some of the same duties, obligations, and values. However, it is not realistic to expect that we can or should appeal to particular religious texts, teachings, or doctrine to address public moral issues that affect people who subscribe to different religious beliefs or have no religious beliefs at all. Thus, the divine command theory cannot provide us with a suitable framework for dealing with ethical dilemmas in research involving human subjects.

3.5 Virtue Ethics

Virtue ethics, like the divine command theory, is a very old view, tracing its history to ancient Greece. Plato and his student Aristotle (384–322 BCE) held that morality consists in living a good life and being a morally good (or virtuous) person. Something is good, according to Aristotle, if it performs its function well. A good flute player plays the flute well, a good runner runs well, and so on. A good human being is one who performs human functions well. People have many functions that they share with other living things, such as reproduction, growth, and movement, but only human beings have the ability to reason. Human goodness (or virtue) can be equated with rational activity of the soul, which consists in practicing and developing various good character traits (or virtues), such as courage, moderation, kindness, benevolence, honesty, loyalty, integrity, compassion, and justice. Aristotle held that virtues fall in between two extreme forms of conduct. For example, too little courage

is cowardice, which is a vice; conversely, too much courage is rashness, which is also a vice. Proper courage falls in between cowardice and rashness. Aristotle held that we develop virtue by imitating virtuous conduct we observe in other people: to become a good man (or woman) you must do what the good man does. Aristotle also included practical wisdom among the virtues. Practical wisdom consists in knowing how to act in particular situations. We can use our practical wisdom to determine what a virtuous person would do in various situations (Aristotle 2003).

Although virtue ethics was popular in ancient Greece, it fell out of favor among philosophers during the Enlightenment period until it was revived by Foot (1978), MacIntyre (1984) and other philosophers (Timmons 2002, Pojman 2005). An offshoot of virtue ethics is the ethics of care, developed by psychologist/philosopher Carol Gilligan (Gilligan 1982) based on women's moral experiences. Gilligan's basic premise is that women have very different experiences of morality than men. Women tend to focus on caring relationships, rather than notions of duty, justice, or rights. The ethics of care makes the virtue of care central to morality, so that moral conduct consists in providing, receiving, procuring, and distributing care (Timmons 2002).

Part of the appeal of virtue ethics is that it provides guidance on how one ought to live one's life and the kind of person on ought to be. Most people will readily accept the idea that we ought to strive be kind, just, benevolent, honest, and so on. All of the other theories discussed in this chapter also imply that virtue is an important moral value worth pursuing (Timmons 2002). Virtue ethics is a teleological theory because it holds that morality consists in striving for the goal of virtue. The main problem with virtue ethics is that it lacks a workable decision-making procedure for dealing with ethical dilemmas in which virtues pull in different directions.

For example, suppose that you are the director of a transplant unit at a local hospital network. A heart has become available. Three people on the waiting list for a new heart are immunologically compatible with the heart. All three people have similar prognoses if they receive the heart. There are some other differences, however. The first person is a 32-year-old woman with no family who has been waiting longer for the heart than the others, the second is a 38-year-old man who has a wife and two young children who depend on him, and the third is 55-year old man who owns a small welding company but has no wife or children. Who should receive heart? The virtue theorist has no readily apparent way of dealing with this dilemma, other than to advise us to use our practical wisdom to discern what the virtuous person would do. However, it is not obvious how a virtuous person would decide what to do in this situation. He or she could act according to virtue of benevolence and give heart to the man with the family, since this would probably do the most good. Alternatively, he or she could act according to the virtue of justice and give the heart to the person who has been waiting the longest ("first come, first served"). It is possible that different people pursuing virtue would make different choices (Timmons 2002).

This example also illustrates another problem with virtue ethics: it has difficulty dealing with complex questions of social justice or public policy, which often arise in biomedicine and biomedical research. (See Box 3.1 for discussion of justice.) It is not at all clear, for example, what it would mean to practice the virtue of justice

Box 3.1: Justice

Justice is an important issue that often arises in human research ethics. The authors of the *Belmont Report* argued that justice was a fundamental principle of research ethics which requires that the benefits and burdens of research be distributed fairly (National Commission 1979). However, the authors of the report had very little to say about how to distribute the benefits and burdens of research.

Justice involves giving people what they deserve. There are four main types of justice: distributive (or social and economic) justice, which addresses the distributions of basic goods (e.g. income, wealth, opportunities, health care, etc.) in society; retributive (or criminal) justice, which deals with crime and punishment; and restorative justice, which deals with making amends for wrongs; and procedural justice, which deals with the fairness of the procedures used to decisions pertaining to distributive, retributive, or restorative justice (Sandel 2010). Some of the influential theories of distributive justice include: egalitarianism, an extreme form of which (i.e. Marxism) holds that basic goods should be distributed equally; libertarianism, which holds that basic goods should be distributed according to a fair procedure which honors property rights and rewards talent and merit; utilitarianism, which holds that basic goods should be distributed in a way that maximizes society's overall utility; and Rawlsian egalitarianism, which holds that basic goods should be distributed according to Rawls' two principles of justice (Sandel 2010).

To understand the difference between these theories, consider three societies (see Fig. 3.3). In society A, wealth is distributed equally between four quartiles and the total wealth is 60. In society B, wealth is distributed very unequally and the total wealth is 150. In society C, wealth is distributed unequally but the worst-off members in society C have more wealth than they do in society C, although the total wealth (140) is less than society B. Which distribution of wealth is the most just? Extreme egalitarians would say that society A is the most just because wealth is distributed equally. Utilitarians would say that society B has the most justice because it has the most total wealth. Libertarians say that whatever wealth distribution has arisen by a fair process which honors property rights is the most fair. For libertarians, huge differences in the distribution of basic goods are acceptable if they result from a fair process. For Rawlsians, society C would be if the most just because the worst-off members of society do the best in society C. The least wealthy quartile has 20 units of wealth in society C and only 15 in society A. According to Rawls, moral and political rights should be distributed equally in society. Other primary goods, such as income and wealth, can be distributed unequally only if the distribution benefits the least-advantaged members of the society and there is equality of opportunity (Rawls 1971).

It may be the case that different approaches to justice are appropriate in different contexts. For example, most people would agree that grades for per

(continued)

Box 3.1 (continued)
formance in a class should be distributed according to merit, not on the basis of equality. However, we would probably say that vital organs should not be distributed on the basis of merit but by means of a system which recognizes that people have equal moral value (i.e. a lottery or a "first come, first served" approach). Most people would view a utilitarian form of distributing health care known as triage to be a fair way of responding to a public health emergency in which medical resources are scarce. In performing triage one distinguishes between three types of patients: (a) people are so sick or injured that they will probably die soon, even if they receive treatment; (b) people who are healthy enough to do without treat for a while; and (c) people who are significantly sick or injured and can benefit from immediate treatment. In triage, one treats patients from group (c) first because this will make the best use of limited medical resources. Patients from group (b) are treated later, and those from group (a) may receive only comfort/supportive care.

when allocating organs to patients. Would justice require that the person waiting the longest receive a chance at the organ first, or should people waiting in line enter a lottery? Does justice require that we give an organ to the person who is the most meritorious? When it comes to public policy, the answers we are looking for must be couched in terms of rules. For example, if the hospital wants to develop transplantation policies it will need to consider some rules for transplantation. Since virtue ethics focus on moral virtues, as opposed to moral rules, its ability to provide policy guidance is somewhat limited. Virtue ethics seems to be most applicable to the realm of personal relationships.

Another problem is that virtue ethics is self-centered because it construes moral conduct as a type of self-improvement (Athanassoulis 2015). We should act morally so that we can be better people. Without a doubt, improving ourselves helps us to get along with others, but one might argue that morality consists in more than in being a good person: it also includes doing the right thing for the right reason. As we shall see below, Kantians take this approach to morality. Even those who do not adopt the Kantian view might wonder whether there is more to morality than practicing virtue (Timmons 2002).

Although virtue ethics provides us with some insight into what it means to live a morally good life and offers useful guidance for how we should handle personal relationships, it has difficulty dealing with the ethical dilemmas that arise in complex and novel situations involving many people, which often occur in research with human subjects. Virtue ethics may compliment other approaches to ethical conduct, but it does not provide us with the decision-making framework we are seeking (Resnik 2012b).

3.6 Natural Law Theory

Natural law theory grounds moral values and duties on human nature. As noted earlier, Aristotle held that virtue is based on our natural reasoning capacity. The natural law theory builds on this idea and holds that human nature determines what is good or bad. For example, St. Thomas Aquinas (1225–1274) held it is part of human nature to need or want four human goods: life, procreation, knowledge, and social relationships. Other goods, such as health, food, shelter, and so on, are valuable as far as they help us attain these basic goods (Aquinas 1988). Things that oppose natural goods, such as disease, ignorance, famine, and suffering are natural evils. The natural law theory is a teleological approach to morality because it holds that our moral obligations are based on the goals of promoting natural goods and avoiding natural evils. Our duty—the moral law—is based on natural law. For example, we have a duty not to commit murder because human life is naturally good. We have an obligation to have children because procreation is naturally good. We should not lie, cheat, steal, betray our friends, or commit adultery, because these acts undermine social relationships (Aquinas 1988; Timmons 2002).

A key problem for the natural law theory, or any moral theory for that matter, is how to deal with moral conflicts. Suppose that someone is threatening me with a knife. Is it justifiable for me to kill in self-defense? My life is a natural good, but should I take another life (which is also a natural good) to save my own? The principle of double-effect is a key pillar of the natural law theory which provides an answer to conflicts involving good and bad effects. According to the principle, it is morally acceptable to perform an action with bad effects if: a) the action itself is not wrong; b) the bad effect may be foreseen but is unintended; and c) the bad effect is proportionate to the good effect. A bad effect would be unintended if it is not sought in itself or as a means to the good effect (Timmons 2002). For example, in the self-defense example, killing the attacker would be morally acceptable, provided that the act (i.e. saving one's life) is not wrong, the killing is not intended, and the killing is proportionate (e.g., no more violence is used than is necessary to save one's life).

While the principle of double-effect provides the natural law theory with a way of dealing with moral conflicts (i.e. good vs. bad effects of an action), it has some weaknesses. Chief among these is that it may not be clear what makes a bad effect proportionate to the good outcome (Timmons 2002). To determine proportionality, one must engage in moral priority setting: what is more important: to promote the good or avoid the bad? The natural law theory does not have any simple answers to this question. For example, suppose that a man is terminally ill and suffering a great deal. To ease the patient's suffering, the doctors prescribe him heavy doses of opioid medications which relieve his suffering but hasten his death. Would this act of "terminal sedation" be unethical? The answer depends, in part, on how quickly the doctors hasten the patient's death. If the patient has only a week or so to live, and the doctors shorten his life by one day, most people would agree that this would be acceptable. But suppose the patient has 6 months to live and they shorten his life by 5 months. Most people would probably view this as murder or unjustified euthanasia. Therefore, to decide upon the morally correct course of action, one must consider

two competing values: promoting life and relieving suffering (Billings 2011). If one applied the doctrine of double-effect to the HIV prevention trials discussed in Chap. 1, one would need to determine whether the bad effects (i.e. not treating HIV patients in the placebo group) would be proportionate to the good (i.e. developing a cheaper means of preventing perinatal HIV transmission).

Part of the appeal of the natural law theory is that it attempts to provide an objective and universal foundation for morality in human nature (Gert 2004). Unfortunately, what makes the theory attractive to empirically-inclined philosophers and ethicists may also be its downfall. While psychology, biology, sociology, anthropology, and other sciences can provide us with some insights into morality (Greene 2013), we cannot easily derive normative, moral conclusions from descriptions of human nature (Barcalow 1994). The mere fact that something is natural does not make it good or right. For example, aggression is part of human nature (Lorenz 1967). But the fact that aggression is natural does not make aggressive acts right. Aggression may be justified to defend one's self but not steal someone's property. We need a moral standard independent of nature to tell us when aggression is and is not justified. Also, the fact that something is unnatural does not make it wrong. It is not wrong, one might argue, for a fertile couple to decide not to have children, even though this choice would go against their natural capacities. Indeed, if we accepted a strongly naturalistic approach to ethics, then would have to regard much of our technology and medicine as immoral because it changes or enhances natural human functions and capacities. While we can draw upon nature to provide us with a source of value—for example most people would agree that life and health are valuable—we should not use nature as the sole arbiter of morality.

3.7 Utilitarianism

English philosophers Jeremy Bentham (1748–1832) and John Stuart Mill (1806–1873) proposed an influential theory known as utilitarianism. According to Mill, utilitarianism is:

> The creed which accepts the foundation of morals or "utility" or "the greatest happiness principle" holds that actions are right in proportion as they tend to promote happiness; wrong as they tend to promote the reverse of happiness (Mill 1979:7).

On this view, morally right conduct consists in promoting the greatest net good for the greatest number of people, where the good is equated with happiness. Mill argued that everything we regard as good is either part of happiness (e.g. knowledge or virtue) or is a means to obtaining happiness (e.g. health, food). Mill did not equate happiness with mere physical pleasure and distinguished between different types of happiness. Happiness could include pleasures of the intellect, such as reading, writing poetry, enjoying music, and so on (Mill 1979). Modern utilitarians, such as Singer (1979), Brink (1989), Brandt (1998) and Hooker (2000), do not equate the good with happiness, because happiness can be difficult to define. Some

equate the good with advancement of welfare, fulfillment of interests, or satisfaction of preferences. Others, such as Brink (1989) accept a plurality of goods, so that promoting the good consists in promoting many different things that we would want or need, such as well-being, health, wealth, social relationships, and so on. Utilitarianism can be characterized as a teleological theory because it holds that morality is goal-directed (Timmons 2002).

Mill held that the principle of utility is a basic moral axiom which is not capable of proof in the ordinary sense of the term. Nevertheless, he offered a justification of the principle:

> No reason can be given why the general happiness is desirable, except that each person, so far as he believes it to be attainable, desires his own happiness. This, however, being a fact, we have not only all the proof which the case admits of, but all which is possible to require, that happiness is a good, that each person's happiness is good for that person, and that the general happiness, therefore, a good to the aggregate of persons (Mill 1979:34).

There are some problems with this "proof." For example, Mill moves from the descriptive fact that we desire our own happiness to the normative conclusion that happiness is desirable. But there might be many things which people desire that we would not regard as desirable (i.e. worth desiring or pursuing). For example, some people desire to injure themselves, too eat food or drink alcohol excessively, and so on. Even if we accept the notion that each person's happiness is good, it does not follow that the aggregate happiness is good. Indeed, some would argue that this form or reasoning commits the fallacy of composition: one cannot infer properties of a whole thing from properties of the parts (Timmons 2002). For example, from the premise that all members of society are human beings we cannot conclude that society is a human being.

Other philosophers have offered proofs of the principle of utility similar to Mill's, which we do not need to dwell on too long here (see Brandt 1998; Greene 2013). Our critique will focus, instead, on some of the troubling implications of accepting a principle of utility as a guide to ethical decision-making. Before turning to these critiques, we should discuss the theory's strengths, which are significant. First, the principle of utility captures an important intuition that most of us probably share, i.e. that promoting good consequences does matter in ethics (Timmons 2002; Pojman 2005). For example, most of us would probably agree that, other things being equal, saving 100 lives is better than saving 10, or that killing 100 people is worse than killing 10. Second, utilitarianism, unlike some of the other theories we have examined, offers a clear decision-making procedure. In deciding what one should do, one should consider the likely consequences of the different options and choose the option which is likely to yield the greatest balance of good/bad consequences for the most people. Third, utilitarianism is a highly general theory because it applies to many different ethical problems, including questions involving personal relationships, social justice, and public policy.

One of the critiques of utilitarianism is that it does not give sufficient consideration to the welfare or rights of the individual (Timmons 2002). Consider a famous ethics thought experiment, originally developed by Foot (1978) and Thomson (1985), known as the trolley problem (Greene 2013). (See Fig. 3.2.) Suppose there

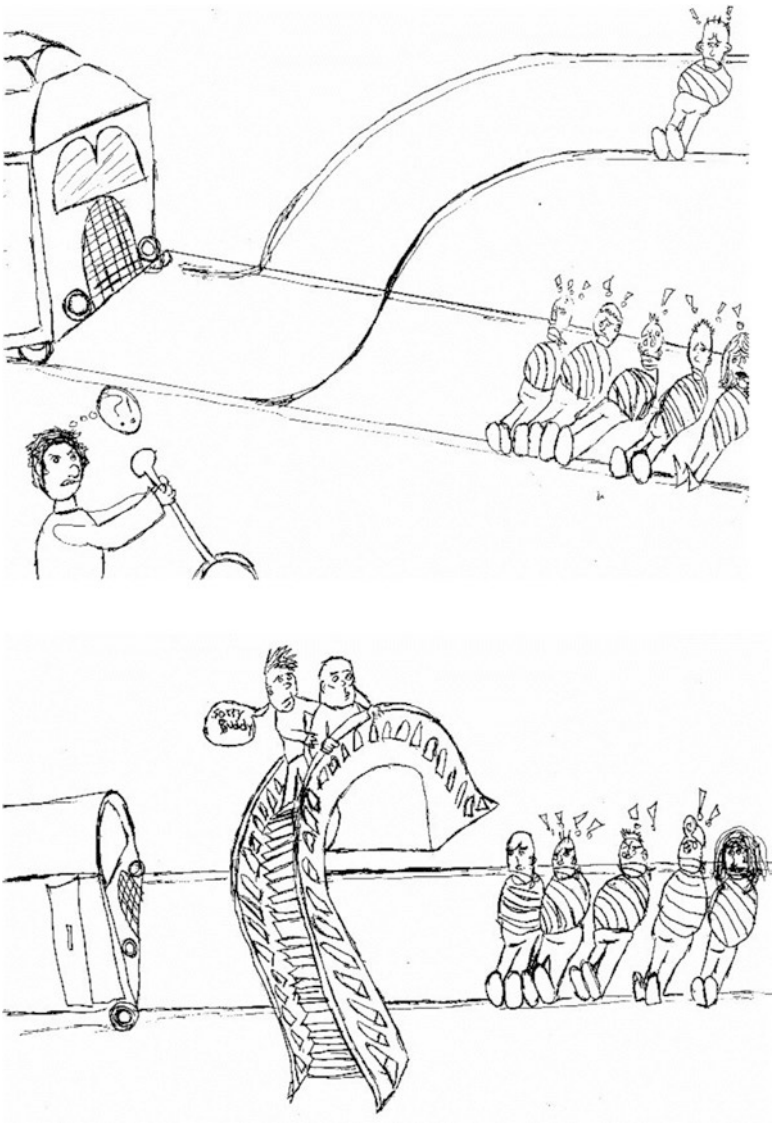

Fig. 3.2 The trolley problem (Used with permission from Peter B. Resnik)

is a runaway trolley heading down the tracks. If it continues on its course, the trolley will kill 5 people who have been tied up and placed on the tracks by a wicked person. There is not enough time to untie the people. However, you can pull a lever which will divert the trolley onto a sidetrack on which one person is tied down. Utilitarianism would tell you to pull the lever to achieve a net total of 4 lives (1 killed, 5 saved), as opposed to doing nothing, which nets −4 lives (5 killed, 1 saved). Psychological studies indicate that about 80% of respondents say that they would

pull the lever (Greene 2013). But let's change the example a little bit. Suppose there is no sidetrack but you can push a large man off a footbridge onto the tracks, which will stop the trolley. In this scenario, about 80% of people say they would not push the man onto the tracks (Greene 2013).[1] We seem to have a strong moral intuition, which runs counter to utilitarian thinking, that there should be some limits on what we may to do to individuals to promote the common good. The ends do not justify the means.[2]

As noted in Chaps. 1 and 2, this type of conflict, i.e. the good/rights of the individual vs. the good of society, often arises in research with human subjects. According to utilitarianism, we should resolve these dilemmas in favor of the good of society, which is promoted by advancing scientific knowledge. The same logic which implies we should kill an innocent person to save five lives would also imply that we should withhold medical treatment from research subjects in placebo control groups to save many lives, even when a treatment is available and they may be significantly harmed by not receiving treatment. It is acceptable for some people to suffer or die as a result of research participation so that others may benefit. However, many people would object to this utilitarian thinking on the grounds that human research subjects should be protected from unnecessary harm or exploitation (Jonas 1985).

Another critique is that utilitarianism does not provide a satisfactory account of social justice because it focuses on aggregate utility rather than the distribution of utility (Greene 2013). For example, consider the distribution of wealth in three societies (see Box 3.1 and Fig. 3.3). Utilitarians would hold that society B is the most just because it has the greatest total wealth, but other theorists would claim that society B is unjust because wealth is distributed very equally (Rawls1971; Timmons 2002).

Utilitarianism also has disturbing implications for criminal justice. Suppose an unidentified man of race A has murdered a man of race B in a town with a history of violent conflict between races A and B. If the police do not arrest a man from race A soon and charge him with a crime, people from race B are likely to start a riot, which would probably cause serious injuries, property damage, and possibly death. To prevent these harmful consequences, the police decide to arrest an innocent man from race A and charge him with a crime. The prosecutor agrees to put him on trial and seek a conviction if necessary. While a utilitarian would endorse this plan to arrest an innocent person to prevent a riot, most people would view it as unjust on the grounds that we should punish people only if we have strong evidence that they have committed a crime. Innocent people should not be punished to calm and angry mob or for any other reason (Greene 2013).

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[1] There are also many variations of this thought experiment. In one variation, the five people are all 90 years old, whereas the one person is only 12; in another variation, the five are strangers, whereas the one is your spouse or child; and in another variation, you can flip a switch that will make a robot push the man onto the tracks (see Greene 2013).

[2] Natural law theorists would be able to distinguish between these two cases. Pulling the switch would be ethical, because the bad effect (i.e. killing one person) would not be intended, whereas pushing the man off the footbridge would be unethical because the bad effect would be intended, since the fat man must be hit by the trolley to stop it. Virtue ethicists could say that pushing the man onto the tracks would be wrong because a virtuous person would not do this.

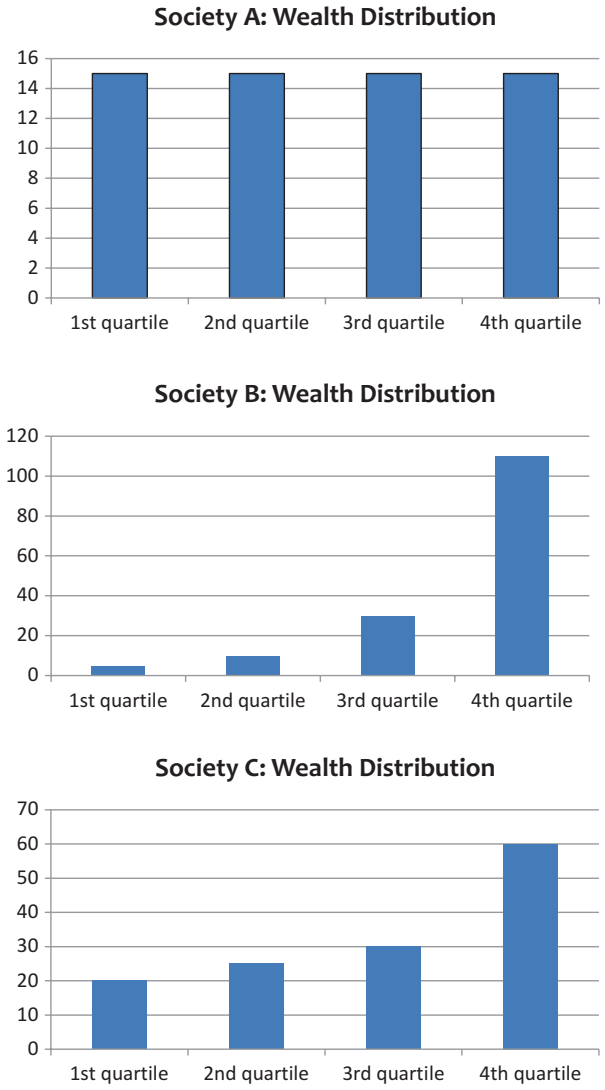

Fig. 3.3 Wealth distribution in three societies

A third critique is that utilitarianism does not give sufficient weight to self-interest or self-care. For example, suppose I have $250 each month leftover after paying my bills. I can spend that money on myself or I can send the money to a charitable organization that helps people who need basic necessities, such as food, health care, etc. If I follow utilitarianism, I should give that money to charity, since this would probably produce more net good. Though the money would produce some utility for me, since my basic needs are already met, it would produce more utility by giving it those who need basic necessities. But it does not end there.

Utilitarianism would also seem to instruct me to continue giving away my income and wealth until I am as deprived as those I am helping (Singer 1972). If one takes utilitarianism seriously, it would seem to demand a great deal from us—some would say too much (Greene 2013).

Another way of putting this point is to say that utilitarianism does not recognize the distinction between what is morally obligatory and what is morally supererogatory. An act is obligatory if it morally required; an act is supererogatory if it goes above and beyond the call of duty. While we might praise you as a moral saint if you give all of your money to help others, we would not say that you would be acting immorally if you failed to do this. Ordinary people are not required to be moral saints. Utilitarianism seems to require that we should all act like moral saints, which seems to place unrealistic and excessive demands on people (Timmons 2002).

Utilitarians have developed responses to these objections, most of which involve distinguishing between act utilitarianism (AU) and rule utilitarianism (RU). According to AU, one should perform the act that maximizes utility, whereas under RU one should follow a rule that maximizes utility (Timmons 2002). Rule-utilitarians argue that counter-intuitive implications of utilitarianism will not occur if one understands the theory as applying to rules instead of actions (Brandt 1998; Hooker 2000; Greene 2013). For example, utilitarianism need not imply that we should push the large man onto the railroad tracks to save five lives because the adverse social consequences of following a rule that required such conduct would outweigh the good results. If we lived in a society when people were always ready to trade one life for five, we would be in constant fear that we might be killed to save someone's life. This fear would undermine human relationships and society would be unable function if we followed such a rule. Rule-utilitarians could argue utilitarianism can promote social justice by accounting for the negative impacts of inequitable distributions of utility. Societies with huge disparities in wealth are likely to have many socioeconomic problems, such as poverty, disease, homelessness, drug abuse, and crime, which negatively impact overall utility. A rule-utilitarian could argue that utility would not be maximized if police and prosecutors followed a rule that required them to accuse innocent people of crimes to quell social unrest, since the adverse effects of such as policy (e.g. increased distrust of the police and fear of the legal system) would outweigh any gains. Finally, rule-utilitarians could argue that utilitarianism can give adequate weight to self-interest and self-care. Society would not be better-off, a rule-utilitarian could argue, if everyone followed a rule which required them to give away virtually income and wealth to help people who are worse-off, since people would lack motivation to work hard (or at all) if this were the moral rule.

While the RU response to these objections to utilitarianism seems reasonable, it may not satisfy the critics of the theory because a great deal hinges on the relationship between the rules and utility (Timmons 2002). RU might recommend different rules, depending on the type of society one lives in and consequences of adopting the rules. For example, people who live in a collectivist society may be better able to accept a rule that mandates taking an innocent life to save five. It could turn out that the negative consequences of following such a rule would not outweigh the positive ones in that society. Critics would argue that individual rights/welfare

should be protected, regardless of the likely consequences of various rules. Likewise, the adverse consequences of inequitable distributions of utility might not materialize in societies in which people are accustomed to large differences in income, wealth, legal rights, and so on, such as societies based on caste systems. Rule-utilitarians could respond to these counterarguments by claiming that the rules entailed by RU are rules for ideal societies, not actual ones (Brandt 1998; Greene 2013). For example, a rule that requires the killing of one innocent person to save five would not promote utility in an ideal society. But this reply leaves one wondering how rule-utilitarians would decide which rules would promote net utility in an ideal society, and how one should characterize an ideal society.

Rule utilitarians must also develop a procedure for adjudicating conflicts among rules when these arise. For example, suppose that RU includes a rule protecting a parent's right to make decisions for his or her child but also a rule allowing the state to mandate vaccinations for children. The rule utilitarian needs a way of deciding which rule should take priority if a parent refuses to allow her child to be vaccinated. The rule utilitarian could argue that all conflicts among rules should be settled by appealing to the principle of utility. While this strategy seems reasonable, it would seem to defeat the entire point of having rules, since utility is the ultimate arbiter when moral conflicts arise. However, the rule utilitarian could argue that rules still have a purpose, since they govern our behavior when we do not face moral dilemmas.

To summarize this section, RU shows some promise as a theory for making ethical decisions concerning research with human subjects. The theory provides a clear decision-making procedure which applies to a variety of complex ethical issues. However, RU has some problems dealing with our moral intuitions concerning the protection of the rights and welfare of individuals, respecting self-interest and self-care, and promoting fair distributions of utility.

3.8 Kantianism

Kant developed a moral theory which continues to have considerable influence. Even philosophers who do not consider themselves Kantians embrace some of his ideas about morality. Kant's theory is deontological because it is duty-based. Kant held that it is an action's connection to the moral law, not the consequences of the action or the character of the actor, which makes the action moral or immoral (Timmons 2002).

As we have seen above, different theories have different accounts of what is good or morally valuable. Philosophers have equated the good with happiness, virtue, knowledge, human life, and so on. Kant held that the only thing which is a good without qualification is a good will. Having a good will is more fundamental than moral virtue, because moral virtues may be used to accomplish immoral goals. For example, a person with a bad will could draw upon his courage or to commit a crime. Likewise, wealth, power, health and other things thought to be good can be

used by someone with a bad will to accomplish bad things. Even happiness is not good without qualification, because the happiness of a bad-willed person would be a bad thing. To even be worthy of happiness, one must have a good will (Kant 1981). Someone with a good will is a person who is motivated to act not by selfish reasons, emotions, or ingrained character traits, but by the desire to do his or her moral duty for duty's sake.

One's duty, according to Kant, is based on a general moral principle known as the categorical imperative (CI). The CI implies various categorical rules (Kant 1981). Categorical rules (or imperatives) are different from hypothetical ones in that they are not directed toward particular ends or goals. The rule (or maxim), "In order to be a good person, I will try to make others happy" would be a hypothetical imperative because it has the goal of developing moral virtue in one's self, whereas the rule "I will help others who are in need" is a categorical imperative because it is not directed toward any particular goal.

Kant's proof of the CI involves the concept of the kingdom of ends (Korsgaard 1996). The kingdom of ends is not a real place but a hypothetical situation in which rational agents decide upon general rules for their society. It is analogous to the idea of a social contract found in the work of Thomas Hobbes (1588–1679), John Locke (1632–1704), Jean Jacques Rousseau (1712–1778) and Rawls (1971). Rational agents have autonomy (or freedom of the will) which means that they are capable of formulating and acting upon moral rules (Kant 1981). The CI is the general rule the rational agents would formulate for themselves in the kingdom of ends. A rational agent could be a human being or a member of another species who has reasoning capacities.

Kant articulated several different versions of the CI. We will focus only on the first two here.[3] According to the universal law version, you should "Act only on that maxim whereby you can will at the same time it should become a universal law (Kant 1981:30)." The key insight behind this version of the CI is that morality is about following universal laws for all rational agents. A rule that applied only to a group of people, community, society, or religious sect would not be a moral rule. Although this version of the CI sounds like the Golden Rule, it is different. Indeed, Kant was critical of the Golden Rule because it depends on the agent's point of view, whereas the CI does not. For example, a masochist who inflicts pain on others would be satisfying the Golden Rule but not the CI because the rule "inflict pain on others" could not become a universal rule for all rational agents.

According to the respect for humanity version, you should "Act in such a way that you treat humanity, whether in your own person or in the person of another, always at the same time as an end and never simply as a means (Kant 1981:36)." The key insight behind this version of the CI is that we should not use rational agents (i.e. humanity) as mere objects or things to achieve certain goals, because rational agents have intrinsic dignity or worth which cannot be traded for or replaced by something else. Deception, fraud, coercion, manipulation, theft, exploitation,

[3] For a discussion of the other versions of the CI and the relationship among the versions, see Hill Jr. (1992).

murder, rape, and many other actions widely regarded as immoral involve violations of human dignity. Incidentally, this version of the CI would prohibit us from pushing someone in front of a runaway trolley to save five lives (Greene 2013).

Kant distinguished between duties to one's self and duties to others (Kant 1981). One has a general duty promote one's own well-being and develop one's talents or skills, and one has a general duty to promote the well-being of other people. One should also treat one's self and other people with respect, i.e. not as a mere end.

Kant also distinguished between perfect and imperfect duties. A perfect duty is absolute rule which has no exceptions. A perfect duty has no exceptions because the negation of the duty could not become a universal law. For example, Kant held that we have a perfect duty to others not to make promise we do not intend to keep because the maxim "I will make a promise I do not intend to keep" could not become a universal law, since if everyone followed this rule we would not trust each other's promises and the institution of promise-keeping would collapse. We have a perfect duty to our self not to commit suicide, because suicide could not become a general rule for all rational agents, since society would cease to exist if suicide became a rule (Kant 1981).

An imperfect duty, by contrast, may have exceptions because the negation of the duty could become a universal law. For example, Kant held that we have an imperfect duty to help others. The maxim "I will not help others" could become a universal law because a society could exist where people do not help each other. However, moral agents would recognize that they would sometimes need help, so they would not will this maxim, i.e. they would not want it to become a universal law. Since the duty to help others is imperfect, we are not obligated to help someone whenever we have the opportunity to do so, because we may have other duties which conflict with this duty, such as an imperfect duty to promote our own well-being. Kantianism does not imply that we should devote so much of our time, wealth, and energy toward helping others that we reduce ourselves to poverty or injure our own health. In deciding whether to help others, we must consider our competing obligations (Kant 1981).

Kantianism has considerable strengths that we should mention before turning to critiques of theory. First, it accounts for our strong intuition that we should not use people as mere things to promote certain ends—even noble ones (Hill Jr. 1992). Most of us would not push someone in front of a runaway trolley to save five lives. The second version of Kant's CI provides us with a way articulating this intuition. Second, Kantianism develops the idea that morality is about following universal rules (Korsgaard 1996). As we saw in the previous section, rule-utilitarians have latched onto this idea to defend utilitarianism against various objections. Rules and principles also play an important role in other moral theories (Timmons 2002). Third, Kant's theory includes duties to one's self and duties to others, so it does not have the counter-intuitive implication that we should sacrifice our own well-being to help others (Timmons 2002). Fourth, Kantian theory provides a framework for thinking about justice. Rawls' defense of the principles of distributive justice was strongly influenced by Kant's conception of a kingdom of ends. Kant also held that punishments should be proportional to the crimes committed and that criminal pro-

cedures should respect human dignity (Hill Jr. 1992). Fifth, the CI implies a general decision procedure for making complex ethical decisions. To resolve a conflict, one can formulate a maxim for a proposed choice and test it against the CI. If the maxim is not consistent with the CI, then one should not make that choice and one should seek another option.

One of the main critiques of Kant's theory is that it appears to imply a kind of a kind of moral absolutism with counterintuitive results. Kant maintained that we have a perfect duty not to lie to others, since lying could not become a universal rule for all rational agents. Lying could not become a universal rule because if everyone lied no one could be trusted to tell the truth. Also, lying to someone fails to respect their humanity (Varden 2010). But what about lying to prevent someone from being killed? Suppose that a would-be murderer comes to our door and they are looking for a person they intend to kill, who happens to be hiding in our house. They ask us if we know where that person is. Should we tell them the truth or a lie? Kant's view implies that we should not lie to the murderer, since we have a perfect duty not lie but only an imperfect duty to help others. Kant, himself, discusses this very example and argues that we should not lie to the would-be murderer (Varden 2010). Most people, however, would probably say that it we should lie to a would-be murder to save someone's life (Timmons 2002). Thus, Kant's view has a striking, counterintuitive implication. Defenders of Kantianism have argued that his theory need not have this bewildering result (Varden 2010). If our maxim is a highly general rule, e.g. "I will lie whenever the situation demands it," then this maxim could not become a general law. If our maxim is more specific, e.g. "I will lie to a would-be murder who is planning to kill someone," then this maxim could become a general law, since adopting this maxim as a rule for conduct would not destroy the practice of truth-telling, because we would only rarely be in a situation in which we lie to a would-be murderer to save someone's life.

This reply to the objection that Kant's view is excessively absolutist brings to light another problem with the theory, namely, that a great deal depends on how we formulate maxims we test against the CI (O'Neill 1989, Timmons 2002). Highly general maxims, e.g. "never lie," or "never break a promise," may sometimes have counterintuitive implications, whereas more specific maxims may not have such implications. So how should we decide which maxim to test when considering our moral duties? Testing only highly specific maxims might allow us to avoid the counterintuitive implications of Kantianism, but this strategy would undermine the very purpose of the CI, which is to provide us with categorical moral rules. The more specific a maxim becomes, the more likely it is to be hypothetical or goal-directed.

Another problem with Kant's theory is that it does not provide us with adequate guidance for resolving conflicts of duties. The theory can deal with conflicts of perfect and imperfect duties, because perfect duties take precedence (Timmons 2002). However, conflicts between imperfect duties can pose problems. Suppose I have $250 leftover after paying my bills. I could give the money to a charity or I could use the money to buy myself some exercise equipment. Since duties to help others or one's self are both imperfect, I need a way of deciding which duty should have moral priority. Kantians could argue that I can decide what to do by formulating

different maxims and testing them against the CI, but it is not clear which maxims I should use and why.

Consider the issue, discussed in Chap. 1, of including placebo control groups in clinical trials when there is known effective treatment for the disease. If the clinical trial involves treating people as mere means for benefitting others, then Kantianism implies that the trial would be unethical. A clinical trial which enrolled human subjects without their consent would be treating the subjects as mere means and would be unethical, on a Kantian view. However, the dilemmas we are interested in addressing do not involve violations of informed consent. The subjects have presumably consented to being randomly assigned to receive the treatment under investigation or a placebo. These dilemmas involve conflicts between imperfect duties: the duty to help subjects with the disease in the placebo group versus the duty to help perhaps many more people by developing scientific knowledge concerning the treatment under investigation. Kantianism would also appear to have no readily available answer on how to resolve this dilemma other than to instruct us to consider different maxims and test them against the CI.

To summarize this section, Kantianism, like RU, also shows some promise as a theory for making ethical decisions concerning research with human subjects. The theory provides a decision-making procedure which can deal with a variety of complex ethical issues and accounts for our intuition that we should not treat people as mere means to promote certain goals. It also instructs us to think about moral choices in terms of applicable rules or principles. However, Kantianism, like the other theories we have considered, has some significant weaknesses. Kantianism seems to imply a kind of moral absolutism with counterintuitive results. It can be difficult to apply Kantian theory to practical problems because a great deal hinges on how one formulates the maxims that one tests against the CI. Kantianism also does not provide us with a straightforward way of resolving conflicts of among imperfect duties. Thus, although Kantianism is by far the most sophisticated moral theory we have considered in this chapter, like the other theories, it has difficulty resolving moral conflicts.

3.9 Natural Rights Theories

We have mentioned rights at various points in this book without exploring this concept in any detail. We will now consider moral theories which focus on rights. Before we do, we need to say a few words about moral rights. A right is an entitlement an individual has to be treated by other people or society in a certain way. For example, if I have a right to life, then other people have a duty not to kill me. Rights have at least two functions: (a) to protect an individual's interests and (b) to give an individual a sphere of influence. For example, my property rights pertaining to my house protect my interests in that house and give me dominion over the house (Wenar 2015).

Legal rights, as established in federal or state constitutions and other legal documents, are different from moral rights because legal rights are enforced by the coercive power of the state, whereas moral rights often are not. Also, one may appeal to moral rights to defend or critique legal rights. For example, one might argue that a woman should have a legal right to abortion based on her moral right to control her body (Barcalow 1994). Very often states also enforce widely recognized moral rights, such as the right to life, but the legal right to life is still distinct from the moral right to life.

Most theorists distinguish between positive and negative rights. Negative rights are rights to be left alone: one can honor a negative right simply by not interfering with or violating that right. For example, the right to life, understood negatively, is simply a right not to be killed. Positive rights, in contrast, are rights to be provided with a good or service. To honor a positive right, one must do something to or for someone (Barcalow 1994; Wenar 2015). For example, many state governments recognize that all school-age children have a right to education. To implement this right, state and local governments must build schools, hire teachers, establish curricula, and develop educational standards. All of this requires considerable funding, which the state acquires through taxation. Most natural rights theorists, such as Nozick (1974) restrict rights to negative rights, since they view the role of government as limited to protecting rights rather than promoting them.

Rights are sometimes described as "trump cards" because they take precedence over other sorts of claims when conflicts occur (Dworkin 1984). For example, if I have a right to free speech, I could assert that this right takes precedence over society's interest in restricting my speech to prevent harm. However, "trump" is probably too strong a word to describe how rights function in argumentation, since most theorists agree that rights can sometimes be restricted when they conflict with other rights or with important social goals (Sinnott-Armstrong 1996; Wenar 2015). A better way of viewing the issue is to say that rights establish a burden of proof: for example, if I have a right to free speech, then the government must produce a compelling argument to justify restricting my speech. The importance of the right at issue determines the level of the burden of proof. For example, the U.S. courts apply a burden of proof known as strict scrutiny to government limitations on some of the rights protected by the Constitution, such as freedom of speech or religion. Under the strict scrutiny test, the government must establish that it has a compelling public interest in restricting the right and that it will use the least burdensome means to restrict it (Barron and Dienes 2013).

Several of the theories we have examined thus far can support moral rights. For Kantians, moral rules stemming from the CI imply moral rights. For example, if I have a duty not lie to other people, then they have right not to be lied to by me. Also, the respect for humanity version of the CI can be interpreted as establishing a general right to respectful treatment (Barcalow 1994; Hill Jr. 1992). Rule utilitarians support individual rights insofar as rules which honor rights promote utility. For example, in *On Liberty* Mill (1978) defended many of the freedoms recognized by natural rights theorists on the grounds that allowing people to make their own choices generally produces more net utility than restricting their freedom for their

own good. However, as we have seen, utilitarian protections for rights could easily erode if utility is better served by restricting rights (Timmons 2002).

Natural rights theorists do not justify rights by appealing to moral duties or utility, since they regard human rights as foundational. Natural rights theorists base morality on some fundamental rights they claim are shared by all human beings, such as rights to life, liberty and property. The right to liberty typically includes the right to freedom of thought, speech, action, association, religion, and peaceful assembly (Nozick 1974). The natural rights approach takes its inspiration from seventeenth century philosopher John Locke's political theory. Locke (1980) argued that all human beings are endowed with certain natural rights by their Creator. While modern natural rights theorists, such as Nozick (1974) and Thomson (1992), do not claim that rights come from God, they do treat rights as foundational. Natural rights theories are usually classified as deontological because they hold that morality is not goal-directed.

Locke used the social contract idea to give an account of the function of government and its authority to restrict rights. Nozick (1974) also appeals to this idea in his moral and political philosophy. According to Locke, in a hypothetical time before the existence of civil society known as the state of nature, people have the authority to enforce their own natural rights. For example, in the state of nature if someone steals my property, I would have the authority to retrieve my property and punish the person who took it. As Hobbes (2006) observed, life in the state of nature can be very difficult and dangerous, since we may easily fall prey to theft, rape, murder, and other violations of our rights, and we may need to devote considerable resources toward protecting our rights. People recognize that it is in their self-interest to form a government to protect their rights and to benefit from social cooperation (Locke 1980; Nozick 1974; Hobbes 2006). Thus, the sole function of government, under this theory, is to protect our natural rights (Locke1980; Nozick 1974). The founding fathers of the U.S. government took inspiration from Locke's political writings. The second paragraph of the Declaration of Independence (1976) reads:

> We hold these truths to be self-evident, that all men are created equal, that they are endowed by their Creator with certain unalienable Rights, that among these are Life, Liberty and the pursuit of Happiness.–That to secure these rights, Governments are instituted among Men, deriving their just powers from the consent of the governed…

Natural rights theories appeal to our strongly held intuition that all human beings have some basic rights that should be protected. Some philosophers have challenged this idea, arguing that rights must be justified and cannot simply be assumed as morally foundational (Fagan 2015). I will not dwell on that issue, since the other moral theories we have reviewed also make some basic assumptions which could be questioned. For example, utilitarians treat the principle of utility as a basic axiom of moral theory, and Kantians regard the CI as foundational. All moral theories, it would seem, must make some basic assumptions that are accepted without further argument (Timmons 2002). My critiques will focus instead on the difficulties with applying the natural rights view to ethical issues and dilemmas.

All of the theories we have examined must confront the problem of how to resolve moral conflicts. Natural rights theorists must provide a way to resolve conflicts involving rights, which could include conflicts between different rights-holders or conflicts between rights and public interests (Sinnott-Armstrong 1996; Wenar 2015). For example, suppose that I own some farmland and I want to start raising pigs. My neighbors do not want me to raise pigs because they are concerned about the stench from the animals and possible adverse health impacts (such as increased risks of respiratory illnesses). This dispute would involve a conflict between my right to use my property and my neighbors' rights not be harmed (by possible adverse the health impacts) or offended (by the smell). For another example, suppose that the state determines that all children should be vaccinated against an infectious disease to protect the public's health. Some parents do not want their children to be vaccinated, however, because they are concerned about possible adverse health effects of the vaccine. This dispute would involve a conflict between parental rights concerning child-rearing and the state's interest in promoting children's health.

Natural rights theorists have proposed different strategies for handling conflicts involving rights. One strategy is to develop a list of exceptions for a right (Oberdiek 2008). For example, the definition of the right to free speech could include various exceptions that specify when speech can be restricted, why, and how. One problem with this approach is the list of possible exceptions may be limitless, because new exceptions might need to be included when the situation demands it. Also, this approach could leave rights so riddled with exceptions that they would become meaningless (Thomson 1992). Rather than creating a list of exceptions, some natural rights theorists prefer to develop tests for balancing the rights and interests at issue, acknowledging that the burden of proof still falls on those who propose to restrict rights (Thomson 1992). This procedure for dealing with conflicts involving rights would involve the kind of priority-setting addressed elsewhere in this chapter.

Some have criticized rights-based approaches on the grounds that they interfere with productive dialogue on moral issues. When someone asserts that they have a right at stake in a moral issue, this often functions to stop debate rather than encouraging the kind of deliberation necessary for a fair and effective resolution of the issue (Glendon 1991). Rights can stop debate because, as we noted earlier, they function like moral trump cards. When someone claims that they have a right at stake, the burden of proof then falls on the party to give a convincing reason for restricting that right, which may result in a stand-off, since each side may assert that their argument is stronger.

Another objection to rights-based approaches is that they ignore our moral duties and responsibilities (Glendon 1991). These approaches tend to skew the moral discussion in the direction of what other people (or society) owe to the individual as opposed to what the individual owes to others. This distortion is especially pronounced in approaches which defend only negative rights, because no one has a duty to do anything for anyone else on this type of view (Callahan 1981). Of course, all approaches, including the natural rights approach, imply that we may acquire obligations to help others as a result informal agreements, legal contracts, or relationships that we voluntarily undertake. For example, a physician who agrees to care for

a patient has a moral obligation to help the patient as a result of this relationship. But these obligations are different from obligations to help strangers. Other moral theories that we have considered, such as Kantianism and utilitarianism, hold that we have substantial moral obligations to benefit other people with whom we do not have an agreement, contract, or relationship. As we saw in the discussion of the controversial HIV prevention trials in Chap. 1, investigators' obligations to benefit research subjects can be an important issue in placebo-controlled studies.

To summarize this section, the natural rights theory provides a way of articulating our strongly held moral intuition that all human beings have some basic moral rights. However, it has difficulties handling the moral conflicts that arise when rights collide with each other or with public goods. Though some theorists have proposed strategies for dealing with these conflicts, these ultimately involve the kind of priority-setting that occurs in other theories. Fair and effective priority-setting may be more difficult for the rights-based approach than other theories, because rights-claims tend to skew the debate in the direction of protecting individual interests.

3.10 Pluralistic Theories

The final type of theory we will examine combines insights from several different theories to form a pluralistic account of morality. Pluralistic theories hold that morality is founded on several (perhaps many) independent moral principles which have intuitive appeal. Pluralistic theories often include teleological and deontological elements (Timmons 2002). Scottish philosopher W.D. Ross (1877–1971) pioneered this approach but several other prominent theorists, including Rawls, Tom Beauchamp, and James Childress have also defended pluralistic theories (Rawls1971; Beauchamp and Childress 2012; Resnik 2012a; Shamoo and Resnik 2015). The *Belmont Report* can also be viewed as a pluralistic approach to morality because it articulates three independent principles, i.e. respect for persons, beneficence, and justice. Pluralists hold that there is no meta-principle for ranking the principles, though Beauchamp and Childress (2012) declare that autonomy should generally be given more weight than other principles.

Ross (1930) argued that morality is based on seven principles which imply *prima facie* duties or obligations. The duties are *prima facie* insofar as we should obey them when other things are equal, i.e. when there are no conflicting moral duties. Our actual duty, according to Ross, is what we should do when there is no stronger, conflicting duty. Ross' *prima facie* duties can be grouped as follows (Ross 1930; Timmons 2002):

- Duties of fidelity: keeping promises, telling the truth.
- Duties of reparation: amending past wrongs one has committed.
- Duties of gratitude: expressing gratitude for gifts or help that one has received.
- Duties of justice: treating people fairly.
- Duties of non-maleficence: not harming others.

- Duties of beneficence: helping others.
- Duties of self-improvement: improving one's character, talents, intelligence, or abilities.

Ross' pluralism combines insights from Kantianism and utilitarianism. Other pluralistic theories may include insights from other theories. For example, pluralism could include principles that deal with human rights or environmental protection (Resnik 2012a).

When *prima facie* duties conflict with each other we must use our moral judgment to decide which duty should take priority (Ross 1930). For example, suppose that I have made a promise to meet a friend for dinner. I have a duty to keep this promise, other things being equal. However, while driving my car on the way to dinner I encounter a pregnant woman who is walking by the side of the road. She signals for me to stop. She has gone into labor and needs a ride to a hospital. Let's assume there is not enough time to call an ambulance for the woman or call my friend. I also have a *prima facie* duty to help this woman. What should I do? According to Ross (and other moral pluralists) I should reach a moral decision by carefully considering my duties, options, and the relevant facts (Beauchamp and Childress 2012). If the woman is in dire need of help, then the correct choice (my actual duty) may be to help her and break my promise. However, if she is not in great need, e.g. if she is not in labor and is just taking a walk and wanted a ride to her friend's house, then maybe I shouldn't break my promise. If other options are available, this might also affect my decision. For example, if I have access to a phone I may be able to call my friend or an ambulance.

One of the advantages of the pluralistic approach is that it requires us to pay careful attention to our available options and the relevant facts in a situation, because these should affect how we set priorities (Beauchamp and Childress 2012). This strategy may be especially helpful in thinking about moral dilemmas involving research with human subjects. For example, one might argue that the acceptability of placebo control groups in clinical trials depends on several key facts, such as (a) the availability of a standard (proven) therapy for the condition, (b) the adverse health impacts of receiving a placebo instead of a standard therapy, and the (c) the subjects' understanding of randomization, placebos, and other concepts related to the trial, (d) the importance of the knowledge expected to be gained from the study, and (e) the strength of the placebo effect (Miller and Brody 2002).

One of the interesting implications of moral pluralism is that there may be more than one morally acceptable solution to an ethical dilemma, because there may different ways of setting priorities. As a result, different people may arrive at different solutions to a moral dilemma because they emphasize different moral principles. As we saw in Chap. 1, well-informed, thoughtful investigators and ethicists took different positions on several ethical controversies concerning research with human subjects. Those who think that a moral theory should deliver one and only one solution to a moral dilemma see the possibility of multiple solutions as a weakness of moral pluralism. Others, however, see this implication as a strength since it allows the theory to acknowledge and explain moral disagreement (Timmons 2002).

Another criticism of moral pluralism is that it is unprincipled because the correct moral decision depends too much on the facts pertaining to a situation. For example, Kantians would say that you should never push an innocent person in front of trolley to save other people. It does not matter whether there are 5, 50, or 5000 lives at stake because you should not treat people as a mere means to achieving certain ends. A pluralist, however, would say that if enough lives are at stake, then pushing someone in front of the trolley would be justified because the facts should impact our moral assessment. Some critics argue that this implication of pluralism undercuts the very point of having moral principles and reduces morality to situational ethics. However, pluralists can reply that moral principles still play an important role in ethics. For example, we should obey moral principles when they do not conflict with other principles. It is only when conflicts arise that we must make decisions based on facts inherent in the situation (Timmons 2002).

A related criticism is that moral pluralism is unsystematic because it lacks a unifying principle or concept, such as the categorical imperative, utility, natural goods, natural rights, or virtue. The theory is a hodge-podge of different views (Gert 2004). While this charge against pluralism has some merit, I would not say that the theory lacks any unity. What unifies the theory is the recognition that we have some basic moral intuitions concerning different rules of conduct, which sometimes conflict. Pluralists see unity in this diversity, whereas other theorists may find this diversity unacceptable.

A final criticism of pluralism is that it is no better than other theories at dealing with ethical conflicts, because solving these dilemmas still depends on exercising moral judgment. Whether one is Kantian, utilitarian, natural law theorist, natural rights theorists, or virtue ethicist, ethical decision-making still depends very much on how one sets priorities in a situation. While this charge has some merit, I would not say that pluralism is no better than other theories at dealing with moral dilemmas. Part of the attraction of pluralism is that it synthesizes insights from other approaches. The pluralist can use ideas from different approaches to make ethical decisions. These ideas may give the pluralist more conceptual resources to work with when thinking about ethical problems. For example, instead of focusing only on duties, rights, virtues, or natural goods, the pluralist can consider all of these ideas in ethical decision-making.

To summarize this section, the main appeal of moral pluralism is that it recognizes that we have strong intuitions concerning some basic moral principles. We can use different moral principles to guide our everyday conduct and moral ethical decisions. Pluralism also includes a workable decision-procedure which applies to a variety of complex issues. While moral pluralism still has some difficulties dealing with ethical dilemmas, other theories also have this problem. Moreover, pluralism may be better than other theories at addressing ethical dilemmas because it has more conceptual resources to draw upon.

3.11 Conclusion: Toward a Decision-Making Framework

In this chapter we have examined five different moral theories (i.e. natural law, utilitarianism, Kantianism, natural rights, and pluralism) which could provide a workable decision-making framework for ethical dilemmas involving research with human subjects. All these potential candidates have strengths and weaknesses: no philosopher has developed a theory which provides effective guidance for practical dilemmas, explains morality, and satisfactorily answers all objections (Timmons 2002). Indeed, we have seen that philosophers have developed a variety of approaches which make different assumptions about the nature of morality and propose different methods for addressing ethical dilemmas. Different theories emphasize different aspects of morality, i.e. following moral rules, promoting moral goods (or values); respecting human rights, or developing moral virtue. The theories also must come to terms with common problems involving moral conflict, e.g. the individual vs. society, fair distribution of benefits and harms, and helping others vs. taking care of one's interests. Recalling our discussion of reflective equilibrium earlier, we may be at a point in time where we are still going back and forth between intuitions and theories (or principles) and we have not yet reached a point where they are in perfect agreement.

Given the current state of scholarship concerning moral theory, some form of pluralism is the most reasonable position. Though pluralism has some weaknesses, it is better able to accommodate conflicting intuitions concerning moral principles and values than the other approaches and has a workable decision procedure (Timmons 2002). The pluralism I employ in this book includes four independent moral principles:

- **Respect for dignityandautonomy**: Treat all human beings as having inherent moral worth; do not restrict an autonomous person's decisions or actions with a sound justification.
- **Non-maleficence**: Avoid causing harm to one's self or others.
- **Beneficence**: Promote the welfare of one's self and others.
- **Justice**: Distribute benefits and harms fairly; use fair procedures to make distributive decisions.

A few comments about these principles are in order. First, the four principles described above are nearly identical Beauchamp and Childress' (2012) principles.[4] One key difference is that Beauchamp and Childress have a principle of respect for autonomy, while I have a principle of respect for dignity and autonomy. I include respect for dignity in this principle because I view dignity as broader than autonomy. Respect for autonomy applies to people as far as they have the ability to make rational decisions. But many people who lack autonomy still have human dignity which should be respected. For example, we should treat infants, young children, and mentally disabled adults as having inherent moral worth even if they lack

[4] For further discussion of these principles and their underlying concepts, see Beauchamp and Childress (2012).

autonomy. The principles are also similar to three described in the *Belmont Report*, except respect for dignity and autonomy replaces for respect for persons, and beneficence and non-maleficence replace beneficence, which are combined in the *Belmont Report*.[5] While some may argue that my approach is not original because I am borrowing heavily from other writers, the uniqueness of my view will become apparent to readers in Chap. 4, when I discuss the role of trust in research ethics.

Second, one can apply these general principles to particular cases by means of a process known as specification (Richardson 2000). Specification involves developing subsidiary rules from general principles. The rules can be more easily applied to cases that the principles. For example, the principles of respect for dignity and autonomy and non-maleficence justify rules for informed consent in research (Brock 2008). Informed consent respects autonomy by giving subjects the right to decide whether to participate in research and it protects subjects from harm by allowing them to refuse to participate in research they judge to be too risky. The requirement to obtain consent justifies other subsidiary rules, e.g. rules pertaining to the disclosure of information or the documentation of consent.

Third, like Beauchamp and Childress, I view these principles as *prima facie* rules of conduct which may conflict in particular cases. Pluralism, like other moral theories, must still deal with the problem of priority-setting when conflicts arise. Beauchamp and Childress do not include a meta-rule for prioritizing the principles, nor do I. Like Beauchamp and Childress, I hold that we might emphasize different principles in different circumstances. Though respect for dignity and autonomy should usually be given the highest priority, there are situations (such as Mill's bridge example, discussed in Chap. 2) when we are justified in restricting a person's decisions or actions for his or her own good. In Chap. 4, I will propose that a fifth principle, the principle of trust, can help investigators, oversight committees, institutions, and funding agencies set priorities in research with human subjects when conflicts arise. As I shall explain later, one can decide what to do by appealing to goal of promoting trust in research with human subjects. Although this fifth principle is not a meta-rule for prioritizing principles, it can sometimes tip the scales in favor of one option or another when we must balance conflicting obligations.

[5] The similarity between Beauchamp and Childress' four principles and the *Belmont Report's* three principles is not a mere coincidence, since both of these authors wrote papers for the National Commission and Beauchamp was a staff member (Beauchamp 2005). The Council for the International Organizations of Medical Sciences (2002, 2016) has also adopted the Belmont Report's principles guidelines for ethical research involving human subjects

Chapter 4
Trust as a Foundation for Research with Human Subjects

The previous two chapters have provided some historical and philosophical background to set the stage for the discussions that will take place in this chapter. In Chap. 2, I examined the history of the ethics of research with human subjects and argued that existing regulations and guidelines were adopted to restore and maintain public trust and prevent ethical abuses from occurring again. However, since ethical issues involving conflicts between the rights/welfare of human subjects and the advancement of knowledge will continue to arise when interpreting and applying existing regulations or deciding whether to revise them, we need an ethical decision-making framework to guide policy formation and help us establish priorities. In Chap. 3, I examined some influential moral theories to determine whether they could supply such a framework. I argued that the theories have strengths and weaknesses but that no single theory satisfactorily answers all objections and satisfies all critics, and that the most reasonable position is to adopt some form of moral pluralism. I proposed that four moral principles, similar to those defended by Beauchamp and Childress (2012), can guide ethical decision-making and policy formation. I noted, however, that the pluralistic approach still faces the issue of priority-setting when moral conflicts arise. I suggested that a fifth principle, the principle of trust, can help investigators, oversight committees, institutions, and funding agencies set priorities in research with human subjects when conflicts arise. In this chapter I will elaborate on and defend an approach to research with human subject based on the notion of trust.

4.1 What Is Trust?

Before proceeding further, we should say a few words about trust. Scholars from philosophy, psychology, sociology, economics, and many other disciplines have explored the meaning of trust and offered proposed different definitions of this

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concept, some of which are technical or esoteric (Baier 1986; Gambetta 1988; Fukuyama 1995; Blomqvist 1997; Govier 1997; Potter 2002; Hardin 2001). My definition of trust follows common usage of the word found in dictionaries (Merriam-Webster 2017). I define 'trust' as "relying on a person or group of people to act or behave ethically, professionally, competently, or skillfully." To rely on something is to depend on it and plan accordingly. The group of people that one trusts could be very small or very large (e.g. a corporation, government organization, profession, etc.). The relying party could be a person or group of people. For example, when I trust a bank with my money, I rely on the bank to keep my money safe. When I trust a doctor to operate on my torn rotator cuff, I trust that he or she will perform the operation correctly, according to the standard of care. When two countries trust each other to follow a peace treaty, they trust each other to abide by the terms of the treaty.

Trust may pertain to specifically-defined behaviors, e.g. when two people sign a contract, they trust each other to perform actions describe in the agreement; or it may pertain to general behaviors, e.g. when I go to the doctor for a checkup, I trust that he or she will examine me according to the standard of care. Trust may be explicit, e.g. when parties sign a contract or reach an informal agreement; or it may be implicit, e.g. when motorists implicitly trust that other drivers will obey the traffic laws and drive safely.

The main function of trust is to promote activities involving social cooperation, such family and social relationships, business, banking, manufacturing, education, and scientific research (Fukuyama 1995; Whitbeck 1995; Govier 1997). None of these activities could take place without a great deal of trust among people. Trust is the cement that holds human societies together.

Trust involves risk-taking and vulnerability (Baier 1986; Hall et al. 2001). If you trust another person to act ethically, professionally, competently, or skillfully, you take the risk that they will fail to do so. For example, the patient who trusts a surgeon to repair his rotator cuff takes the risk that the surgeon will do a bad job and make the injury worse. Trust involves vulnerability because the person who trusts someone else can be harmed or exploited by the entrusted person. For example, if you trust a friend with a secret, you make yourself vulnerable to harm or exploitation if the friend shares the secret without permission or uses it against you.

People usually decide to trust others based on evidence of their trustworthiness, which is a type of moral virtue (Potter 2002). Evidence may come from a variety of sources, such as acquaintance with a person or group, or knowledge of a person's or group's reputation, experience, or competence (Tullberg 2008). For example, you might trust a friend with a secret only after learning more about that person's integrity and discretion. You might trust a mechanic to work on your car upon recommendation from a friend. You might trust a dentist to work on your teeth because you believe that the dental profession is generally competent and skilled. A key function of a professional ethics code is to foster the public's trust in members of the profession. Since trust can be difficult to restore when it has been violated, codes and guidelines often emphasize the importance of maintaining trust (Bayles 1988).

Trust has close connections to moral and legal concepts, such truthfulness (trusting people to tell the truth), promise-keeping (trusting people to keep their promises),

fidelity (trusting people to be faithful or loyal), and confidentiality (trusting people to keep information confidential) (Hall et al. 2001). Trust often implies ethical and legal duties since the entrusted person may have an obligation to do what is expected of him or her. For example, the trust you place in a surgeon to operate on your shoulder obligates the surgeon to inform you about the surgery and perform it correctly.

In the law, fiduciary relationships involve a strong degree of trust between the trusting and entrusted party. The entrusted party (i.e. the fiduciary) has legal obligations to act in the best interests of trusting party (Black's Law Dictionary 2001). Some examples of fiduciary relationships include doctor-patient, lawyer-client, trustee-beneficiary, and guardian-ward.

4.2 Trust in Research Involving Research with Human Subjects

Trust plays an essential role in research with human subjects (Kass et al. 1996; AAMC Task Force on Financial Conflicts of Interest in Clinical Research 2003; Peckman 2006; de Melo-Martín and Ho 2008; Resnik 2010b; Wilson and Hunter 2010). (See Fig. 4.1.) First and foremost, human subjects must be able to trust investigators to act professionally, competently, and ethically (de Melo-Martín and Ho 2008; Resnik 2011b; Wendler 2011). The trust that subjects place in investigators encompasses the entire range of research conduct, including recruitment and informed consent[1]; executing research procedures and methods; minimizing risk; safety monitoring; analyzing, interpreting and publishing data; returning research results; protecting biological samples and private information; using and sharing samples and data; reporting adverse events and unanticipated problems; and complying with regulations, guidelines, and policies. If human subjects distrust investigators, they may decide not to participate in research studies, or, if they do, they

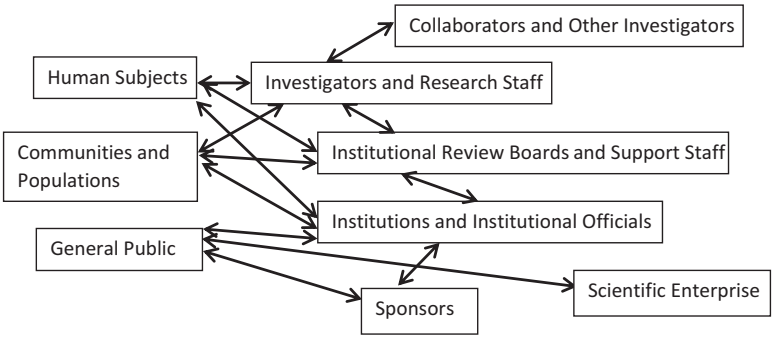

Fig. 4.1 The web of trust in research with human subjects

[1] Chapter 5 will explore informed consent in greater depth.

may not cooperate fully with the investigator or research staff. In the Havasupai case discussed in Chap. 2, members of the tribe said they would not participate in studies conducted by Arizona State University as a result of the breach of trust which occurred when investigators used their blood samples for purposes they said they had not approved (Mello and Wolf 2010). Many different studies have documented distrust of investigators and research institutions as an important barrier to clinical trial recruitment, especially among minority populations (Mouton et al. 1997; Corbie-Smith et al. 1999; Sengupta et al. 2000; Corbie-Smith et al. 2002; Ford et al. 2008). There is some evidence that African Americans' perceptions of unethical behavior by investigators conducting the Tuskegee syphilis study have negatively impacted their willingness to participate in research (Shavers et al. 2000; Freimuth et al. 2001; Earl and Penney 2001).

Second, the trust between subject and investigator also goes in the other direction: investigators must be able to trust human subjects to tell the truth about medical or other conditions that could disqualify them from participating in a study, comply with study requirements (such as taking medications as directed), and honestly and candidly report symptoms and problems they experience during their participation. There is evidence that research subjects sometimes lie to investigators to qualify for studies or during the course of research (Devine et al. 2013). Deception by research subjects can undermine the integrity of the study and place participants at risk (Resnik and McCann 2015).

Third, research subjects must be able to trust research institutions, since institutions are responsible for overseeing investigators and ensuring that they uphold their professional and ethical obligations (Kass et al. 1996; Hall et al. 2001; Peckman 2006; de Melo-Martín and Ho 2008). In the Havasupai case, members of the tribe lost their trust in the investigators and the research institution. In the Jesse Gelsinger case discussed in Chap. 2, Mr. Gelsinger questioned the university's trustworthiness because he was concerned that its financial interests in the research and lax oversight of the study led to the death of his son (Gelsinger 2008). As noted above, distrust of research institutions can negatively impact study recruitment (Ford et al. 2008). Since institutions designate institutional review boards (IRBs) to oversee research with human subjects, trust in the institution extends to the IRB.

Fourth, communities and populations involved in research must be able to trust institutions and IRBs. Communities can provide important support for human subjects research: for example, community organizations (such as local health departments or clinics) can help with publicity and recruitment and may provide financial and other resources to investigators; and community members may enroll in studies, help with study design or survey development, or serve on committees that oversee research, such as IRBs (O'Fallon and Dearry 2002; Peckman 2006; Horowitz et al. 2002; Holzer et al. 2014). If investigators do not have support from communities and populations, they may have difficulty recruiting subjects or implementing study procedures. The Havasupai case provides an instructive example of the importance of the community's trust, since the breach of trust in the case negatively impacted not just individuals but the entire tribe (Mello and Wolf 2010).

Fifth, investigators must be able to trust each other to behave professionally, competently, and ethically (Whitbeck 1995). Investigators must trust members of their own research team and collaborators to comply with regulations and protocol requirements; collect, report, and analyze data accurately; implement study procedures competently; report adverse events and other problems; and treat other members of the team with respect. Since investigators rely on the published literature to inform their own research, they must be able to trust that other members of the research community will not publish data known to be biased, misleading or fraudulent (Shamoo and Resnik 2015). The research misconduct cases discussed in Chap. 2 involving Roger Poisson, Eric Poehlman, Andrew Wakefield, and Woo Suk Hwang constituted serious betrayals of the trust of members of research teams as well the scientific community. The financial conflicts of interest and other problems related to industry bias discussed in Chap. 2 also had a negative impact on researchers' trust of each other.

Sixth, IRBs must be able to trust investigators to comply with ethical and legal requirements for conducting research with human subjects (Peckman 2006; Klitzman 2015). Although IRBs have the authority to monitor or audit research, they do not have the resources to observe research around-the-clock. Even if resources were available for intensive oversight of research, IRBs should refrain from doing this, as it would undermine investigator morale, interfere with study procedures, and transform the research environment into a police state. After the IRB reviews and approves a study, is must trust the investigator to follow the protocol, seek IRB approval for proposed changes to research, and report unanticipated problems, non-compliance, and adverse events. Trust between investigators and IRBs also goes the other way: investigators must be able to trust IRBs to review their research fairly and competently (Klitzman 2015). They should expect IRBs to provide them with useful criticism and feedback concerning their research and not delay review unnecessarily. Investigators should also expect that IRB members will have a working knowledge of regulations and ethical guidelines, and that they will consult with outside scientists or clinicians if they are reviewing a study which is beyond the scope of their collective knowledge or expertise. Since institutions designate IRBs to oversee research, institutions must also be able to trust IRBs.

Seventh, the general public must be able to trust the research enterprise (Kass et al. 1996; Kelch 2002; Resnik 2010b, 2011b). The public expects: investigators to behave professionally, competently, and ethically; institutions to manage resources carefully and oversee investigators properly; government sponsors to fund worthwhile projects; and the research enterprise to maintain the highest ethical and scientific standards. All of the cases involving abuses of human subjects or ethically questionable behaviors discussed in the Chap. 2 had a negative impact on the public's confidence in investigators, institutions, and the research enterprise. Lack of public trust can negatively impact science by eroding research funding, since citizens and politicians may be unwilling to allocate government money to pay for research they regard as untrustworthy (Resnik 2011b). Although government support for scientific research is not as strong as it once was as a result of budgetary constraints, it still accounts for about one third of all research funding (Shamoo and

Resnik 2015). Researchers need to maintain the public's trust to continue receiving generous funding support.

4.3 Trust as a Foundation for the Ethics of Research with Human Subjects: Some Alternative Views

Clearly, trust is an important value which applies to many aspects of research with human subjects. I will now explain how I think that trust can help to provide a foundation for ethical research with human subjects. Before I articulate this framework more fully, I will discuss three approaches to the ethics of research with human subjects which make use of the concept of trust.

Nearly three decades ago, Robert Veatch (1987) developed a theory of human research ethics which proposed the idea of the patient as a partner in research. Veatch observed that there is a mutual-dependence in clinical research with human subjects: subjects need investigators in to gain access to experimental treatments which may benefit them, and investigators need human subjects in order obtain data and samples used in their research. Investigators depend on human subjects not only to enroll in studies but also to cooperate in study-related activities and procedures. Clinical research could not move forward without the participation of human subjects. Veatch argued that thinking of the relationship between investigators and human subjects as a partnership would provide a moral foundation for research with human subjects. Veatch applied this idea to a variety of topic in research with human subjects, including study design, informed consent, risk minimization, and research involving vulnerable subjects (Veatch 1987). Although Veatch did not discuss the concept of trust in any detail, it is clear that his proposal implies that investigators and human subjects must trust each other, since trust is essential to partnerships.

While I think that Veatch's patient as partner proposal is intriguing, it has a couple of flaws. First, while the patient as partner proposal accounts for many of the types of trust which are important in research with human subjects, it does not address trust between human subjects and research institutions, communities and investigators/institutions, trust among investigators, or trust between the public at large and the research enterprise. Veatch was on the right track with his proposal but he did not go far enough.

Second, the patient as partner idea is not completely apt because research subjects often do not function as full partners. Partnership implies equality of responsibility. For example, two business partners are both responsible for handling the affairs of the business, e.g. keeping records, paying debts, filing taxes, complying with regulations, and so on. One partner may delegate some responsibilities to the other, but they are both ultimately responsible. In most studies involving human subjects, investigators bear the brunt of the legal, ethical, and professional responsibilities associated with the study. Investigators are responsible for complying with IRB-approved protocol and regulations, performing study procedures, col-

lecting data, etc. To be sure, research subjects also have some responsibilities, but not nearly as many as investigators in most cases (Resnik and Ness 2012).

While most types of research do not conform to the partnership model, some come close. In community-based participatory research (CBPR) community members are substantially involved in various aspects of research, including development of study aims and objectives, protocol and survey design, data collection, data interpretation, recruitment, and consent (O'Fallon and Dearry 2002; Horowitz et al. 2002; Holzer et al. 2014). Community members may participate as human subjects, research staff, or advisory board members. CBPR recognizes the valuable role that community members can play in assisting with research that addresses their needs and concerns and has become an influential approach in scientific disciplines that study communities and populations, such epidemiology, and public and environmental health.

In 1996, Nancy Kass and colleagues on the Advisory Committee on Human Radiation Experiments published an article in the *Hastings Center Report* based on interviews with over 1900 outpatients concerning their views about research participation (Kass et al. 1996). Many of the interviewees stressed the importance of the trust they placed in investigators, institutions, and the research enterprise. Kass and her colleagues drew some implications of their interviews for research practice and policy. For example, they argued that clinical investigators should be mindful of the tremendous influence they have over patients who are considering enrollment in research. They urged clinical investigators to describe the benefits and risks of research honestly and realistically and avoid biasing the discussion in favor of enrollment if the benefits are minuscule but the risks are significant. They also urged IRBs to take seriously their responsibilities to protect research subjects from harm and exploitation (Kass et al. 1996). However, Kass and her colleagues did not develop their idea concerning trust as a foundation for research with human subjects in any detail.[2]

Sanchini et al. (2016) recently defended a trust-based approach to informed consent in biobanking. They argue that traditional informed consent is inadequate for donating samples to biobanks, because one may not know what type of research the samples will be used for. They argue that one way to get around this difficulty is to reconceive consent for biobanking as primarily about building trust rather than disclosing information. While the authors proposed some interesting ideas about trust in research with human subjects, they did not articulate a comprehensive theory or approach. (In Chap. 5 I will discuss ethical issues concerning informed consent related to biological samples in more detail.)

A little more than a decade ago, Henry Richardson and Leah Belsky published a seminal paper which employed the concept of partial entrustment to justify ancillary care responsibilities for clinical researchers (Richardson and Belsky 2004).

[2] There have been more recent studies of attitudes toward research participation. See Trauth et al. (2000), Sood et al. (2009), Lemke et al. (2010), Zarate et al. (2016). The point of discussing the Kass et al. (1996) article is that it focuses on attitudes as they relate to trust and suggests that trust may serve as a foundation for ethical responsibilities.

Richardson (2012) later published a book which expanded upon the ideas developed in that paper. Ancillary care is medical care provided to human subjects in a research study beyond what is required to (a) address the study's research questions, (b) protect subjects from harm related to their participation in the study, or (c) redress harms that have occurred as a result of participation (Belsky and Richardson 2004). Ancillary care ranges from simple and inexpensive interventions, such as treating mild skin infections, to complex and expensive interventions, such as performing dental work or providing treatment for cancer. Ancillary-care may include medical testing, diagnosis, treatment, or prevention (Belsky and Richardson 2004). Providing ancillary care can be a significant moral concern when human subjects (such as people living in developing nations) lack access to care outside of their participation in research (Dickert and Wendler 2009).

Federal research regulations and ethics codes provide little guidance concerning ancillary care. The Common Rule does not address ancillary care, but its requirement that the risks of research should be reasonable in relation to expected benefits could be interpreted as providing some support for ancillary care, because ancillary care is a potential benefit to the research subject (Department of Health and Human Services 2009). However, one might challenge this interpretation on the grounds that the benefits mentioned in the Common Rule are benefits related to research participation or the products of research (knowledge), and ancillary care goes beyond these. The Helsinki Declaration also does not mention ancillary care, but its requirement that researchers and host country governments should make provisions that ensuring that all participants have post-trial access to interventions identified as beneficial in a clinical trial could be interpreted supporting ancillary care after a study is completed. However, one could argue that post-trial access to treatments is not ancillary care because ancillary care occurs while a study is still underway. The Council for International Organizations of Medical Sciences (2002, 2016) guidelines state that sponsors are not required to provide health care beyond what is required to conduct research but that providing such care would be morally praiseworthy.

Ancillary care is ethically controversial because it often involves a conflict between promoting the welfare of human subjects and developing scientific knowledge. While ancillary care can provide significant benefits for human subjects, it can also increase the costs of conducting research and possibly interfere with a study's scientific objectives (Resnik 2009a). To provide ancillary care, investigators may need to pay for additional medications, laboratory tests, medical devices, or clinical consultations. To cover these costs, they may need to divert money from other study-related activities, which could hamper their efforts to achieve their scientific objectives (Richardson and Belsky 2004). In some cases providing ancillary care may compromise the validity of the study by biasing health outcomes under investigation. For example, suppose that investigators are conducting a long-term observational study of the effects of aging on mobility. If the investigators provide subjects with medications to treat arthritis, this would benefit them but also potentially bias the outcome of the study.

Richardson and Belsky (2004) argue for providing research subjects with ancillary care in some circumstances based on two considerations. First, they argue that all moral agents, including researchers, have a general duty to rescue those in need of help. For example, if you see someone drowning in a pool you should do something to help them, such as calling a lifeguard or throwing them a life-preserver. The duty of rescue has broad support from moral theories, such as Kantianism or utilitarianism, which hold that we have obligations to promote the welfare of other people. The principle of beneficence also supports a duty to help others (National Commission 1979; Beauchamp and Childress 2012).

Second, Richardson and Belsky (2004) argue that researchers have special duties to benefit research subjects based on the trust subjects justifiably place in them.[3] They call their view the "partial entrustment" approach to distinguish it from the full entrustment view implied by conceiving of the investigator-subject relationship as fiduciary in nature, and the no entrustment view implied by viewing the relationship as purely contractual. According to the fiduciary approach, the investigator-subject relationship is similar to the physician-patient relationship in that investigators have strong moral duties to promote the best interests of research subjects because patients entrust them with their health (Miller and Weijer 2006). The fiduciary view implies that it is unethical to include placebo control groups in clinical trials if an effective therapy is available, because withholding treatment from subjects in the placebo group would violate investigators' fiduciary obligations to provide subjects with optimal medical care (Miller and Weijer 2006). According to the contractual view, the investigator-subject relationship is defined by the terms the parties reach during the consent process (Morreim 2005). If a subject consents to participate in a study without the expectation of any benefits (such as ancillary care) then the investigator is not obligated to provide benefits to the subject. The contractual view implies that including placebo control groups in clinical trials is ethical, even when an effective therapy exists, provided that investigators obtain consent from the subjects and minimize harm to them (Miller and Brody 2002).

Richardson and Belsky (2004) argue that subject's trust in investigators lies somewhere in between the no entrustment and full entrustment. The investigator-subject relationship is more than merely contractual but less than fiduciary. Investigators have some obligations to promote the interests of research subjects but these obligations are not as extensive as the obligations that physicians have toward their patients. They suggest that the investigator-subject relationship is analogous to a legal relationship known as a bailment in which the entrusted party (the bailee) agrees to take care of something for the trusting party (the bailor). For example, if a restaurant provides valet parking, it has an obligation to return your car to you undamaged.

The scope of investigators' ancillary care obligations depends on two factors: discretion and vulnerability (Richardson and Belsky 2004). Discretion, which refers

[3] Richardson and Belsky's view is somewhat different than mine in they do not equate trust with a psychological attitude or state. The fact that one relies on someone else does not create a trust relationship. For there to be an entrustment, one must have a good reason for relying on the entrusted party.

to the extent of the investigator's ability to impact the subject's well-being, is a function of the investigators' knowledge, skills, and available resources. Vulnerability, which refers to the subject's susceptibility to harm or exploitation, is a function of factors such as maturity, mental health, institutionalization, and socioeconomic circumstances. Subjects who do not have access to health care outside of a study may become dependent on clinical investigators for their health care. Richardson and Belsky consider an example of a hypothetical pediatric study in an area of Africa where malaria is endemic (10% of the population is infected). They argue that the investigators have an obligation to diagnose and treat the children for malaria because (1) the malaria parasite is easily detectable by urinalysis, (2) the cost of treating malaria will not hamper the study, (3) the investigators have the expertise and ability to treat malaria, and (4) the children will probably not receive treatment outside of their participation in the study (Richardson and Belsky 2004). They argue, however, that if the costs of diagnosing and treating malaria were much higher, then the investigators would not have an obligation to provide this ancillary care, because this could compromise their ability to carry out the research.

While Richardson and Belsky's partial entrustment idea represents a valuable contribution to the literature on the ethics of research with human subjects, it does not provide us with a satisfactory account of the nature of trust in research with human subjects. The first problem is that Richardson and Belsky do not clearly explain what it means to partially trust someone. Does this mean that you trust them to some degree, ranging from almost no trust to almost complete trust? For example, you might partially trust an acquaintance to keep a secret but fully trust a close friend. Or does partial entrustment mean that you trust someone completely, but only with respect to specific activities? For example, you might trust a real estate agent to give you advice about the market value of a home you intend to buy but not advice about the tax implications of your purchase. The metaphor they use to capture their notion of partial entrustment, i.e. the notion of a bailment, does not accurately represent what they seem to have in mind when they claim that partial entrustment implies ancillary care responsibilities, since a bailor has an obligation only to take care of your property, not to improve it (Black's Law Dictionary 2001).[4] For example, a restaurant that offers valet parking is under no obligation to repair existing damage to your vehicle; it only has an obligation to repair damage that occurs while it is taking care of your vehicle (Resnik 2009a).

A second problem with Richardson and Belsky's view is that it does not provide an accurate account of the type of trust involved when human subjects have limited interactions with investigators. A human subject who completes an anonymous survey, for example, may rightfully expect that the investigator will maintain confidentiality, but he or she would not be entitled to anything more than this, such as ancillary care. A human subject who donates a blood sample for a biobank may only rightfully expect that the investigator maintains confidentiality and performs the blood draw competently, not that the investigator will treat his or her existing medical problems. The partial entrustment view makes the most sense when human

[4] Richardson (2012) drops the bailment metaphor.

subjects have meaningful and sustained interactions with investigators, which often occurs in clinical research, but not in survey research or sample collection studies (Dickert and Wendler 2009).

A third problem with Richardson and Belsky's view is that it focuses on only one aspect of trust related to research with human subjects, namely, the trust subjects place in investigators. While this is certainly an important kind of trust, there are many other types of trust in research with human subjects, including trust between investigators and subjects, trust between subjects and research institutions, trust between communities and investigators, trust between communities and institutions, trust among investigators, and trust between the public and the research enterprise. A comprehensive account of trust in research with human subjects should address all these different types of trust (Peckman 2006).

4.4 Trust as a Foundation for the Ethics of Research with Human Subjects: My View

Having discussed some alternative approaches to trust in research with human subjects, I can now develop my own view. My position builds on the idea that promoting trust is an important goal in research with human subjects which should influence decision-making and policy. The principle of trust can be simply stated as: "Promote trust in research involving human subjects."[5] Promoting trust may include restoring of trust which has been damaged, maintaining trust, or nurturing trust. Trust encompasses all aspects of research with human subjects, including relationships between subjects and investigators, subjects and institutions, communities and investigators, communities and institutions, and relationships among investigators (Peckman 2006; National Health Research Ethics Committee of Nigeria2007). Promoting trust is an overarching goal which applies to investigator-subjects interactions, institutional oversight of research, interactions with communities, as well as storing, sharing, and analyzing samples and data, and funding and publishing research. There are a number of strategies for promoting trust in research with human subjects, which I briefly describe below (see Table 4.1).

[5] It is worth noting that the Nigeria's National Code of Health Research Ethics includes trust as a requirement for approval of research with human subjects. According to the Code: "For research to be ethical, nothing must be done to undermine the trust relationship that is at the heart of the researcher(s)-participant(s) relationships. This requires that there is transparency in all matters relating to the research enterprise including clear description of goals, risks, benefits, alternatives to participation and voluntariness. It is also necessary to determine the social value of the research and engage in creative approaches for effective representations and involvement of researchers and communities in the entire enterprise. Strategies for dynamic and reciprocal collaboration that leads to transformation of essential relationships based on reciprocity are also essential. This trust principle encourages the engagement of individual participants and communities, respects local sociocultural values and encourages the provision of relevant and timely feedback to communities (National Health Research Ethics Committee of Nigeria 2007)."

Table 4.1 Strategies for promoting trust in research with human subjects

Type of trust	Strategy
Subject-investigator	Informed consent
	Transparency
	Respectfulness
	Confidentiality
	Compliance with regulations/guidelines
	Competence/professionalism
	Management of conflicts of interest
Subject-institution	Institutional oversight
	Leadership
	Policy development (e.g. SOPs, guidelines)
	Compensation for injury
Community-institution	Community engagement
	Community representation on the IRB
	Accountability
	Leadership
	Management of conflicts of interest
	Policy development (e.g. SOPs, guidelines)
Investigator-investigator	Research ethics education/training
	Policy development
	Support for ethical oversight of research
	Leadership
	Management of conflicts of interest
IRB-investigator	Education and training in research ethics
	Investigator-IRB engagement
	Accountability
	Transparency
	Policy development
Public-research enterprise	Public engagement
	Accountability
	Transparency
	Policy development
	Management of conflicts of interest
	Research ethics education/training

4.5 Promoting Trust in Research with Human Subjects

Informed consent can play an important role in promoting trust between human subjects and investigators. During the consent process, investigators can assure subjects that they will treat them with respect, safeguard their confidential private information and biological samples, protect them from avoidable harm, and follow ethical and legal rules and guidelines. They can assure subjects that they are well-qualified, by education or experience, to conduct research per scientific and professional standards. Investigators should view informed consent as a process for

building trust, not just as the signing of a form (Berg et al. 2001). Investigators should provide relevant information to subjects and give them opportunity to ask questions and discuss their concerns. They should inform subjects who to contact if they are injured in research or want to withdraw from a study. If subjects are harmed in research, investigators should help them obtain medical care. Investigators should honestly and openly communicate with subjects during the entire course of research, including recruitment, enrollment, and follow-up. Communication with may also include appointment reminders, newsletters, and thank you or follow-up letters, emails, or phone calls. All forms of communication, including consent, should be transparent, i.e. information should be honestly and openly shared. For their part, subjects should complete research activities appropriately and on time; answer screening and survey questions truthfully; and take medications as directed (Resnik and Ness 2012). Subjects should inform investigators if they cannot make a scheduled appointment or are uncomfortable about participating in some aspect of a study.

Research institutions can promote research subjects' trust be ensuring that proper oversight mechanisms are in place for reviewing and overseeing research. Responsibility for oversight of research should extend beyond the IRB and include institutional officials, support staff, and investigators (Institute of Medicine 2002a, b). Institutional officials should understand the importance of proper oversight of research with human subjects and should be aware of relevant regulations, policies, and procedures. They should take a leadership role in research oversight and emphasize the importance of adhering to legal, ethical, and professional standards. Institutional officials should provide adequate resources to support the human research protection program (HRPP) and should also seek accreditation for the HRPP. Institutional officials manage conflicts of interest wisely and ensure that research is protected from outside corrupting influences (Kelch 2002). Institutions should also develop policies and standard operating procedures for overseeing research with human subjects, have mechanisms in place for dealing with subjects' complaints and concerns, and fund educational opportunities for investigators, support staff, and IRB members. Institutions should also provide subjects with compensation for research-related injuries, such as medical care (Institute of Medicine 2002a, b).

Community engagement is an important strategy institutions can use to promote the community's trust (Anderson and Solomon 2013; Council for International Organizations of Medical Sciences 2016). Institutions should conduct outreach activities that inform community members about the research conducted at the institution, opportunities to participate, and oversight mechanisms (Holzer et al. 2014; Bromley et al. 2015). Outreach activities may include educational forums, such as conferences, focus groups, or lectures open to the public; as well as sharing of information on websites and in newsletters, press releases, and interviews with the local media. Engagement should include more than information-sharing, but should also involve the solicitation of input from the community. Community members should have the opportunity to expresses their needs, interests, and concerns related to research with human subjects to institutional officials, investigators, and the IRB. Institutional officials should ensure that IRBs and other oversight committees have adequate representation from the community. Investigators should also consider involving community members in the planning and implementation of studies,

as community members may provide valuable insights into recruitment, consent, and research design. Investigators and institutional officials should be accountable to the community, i.e. they should take responsibility for problems that occur in research and should be prepared to answer questions from community members or apologize if warranted.

To promote trust among investigators, institutions should support education and training in research ethics for students, investigators, and staff (Shamoo and Resnik 2015). Education and training should include a variety of topics related to conducting research according to ethical and scientific standards, including misconduct (i.e. data fabrication or falsification and plagiarism), data storage and sharing, conflict of interest, peer review, mentoring and supervision, reproducibility and bias, publication and data sharing, authorship, collaboration, and so on. Institutions, professional associations, and journals should also develop policies or guidelines pertaining to these topics. Institutions should also provide adequate support for overseeing the integrity of research and investigating allegations of research misconduct or other ethical problems. Institutions should also hire research staff (such as ethics or compliance officers) to oversee educational/training activities and consult with students, investigators, and staff on research ethics issues. Institutional leaders should stress the importance of research integrity in the communications with investigators, students, and staff and should endorse ethics education and training activities.

To promote trust between IRBs and investigators, investigators, research staff, and IRB members should receive education/training that focuses on human research ethics. Education should include an initial orientation to ethical and regulatory issues in research with human subjects as well as annual updates concerning changes in regulations, guidelines or emerging issues. IRBs should invite investigators and research staff to attend IRB meetings, and IRB chairs should encourage investigators to talk to them about human research issues, problems, or concerns. IRBs should also periodically survey investigators concerning the perceptions of the IRB review process.[6] IRB decision-making should be transparent and accountable to investigators. For example, IRBs should clearly explain their decisions to investigators. If an investigator disagrees with a decision, the IRB should inform the investigator that he or she the right to ask the IRB to reconsider its decision. IRB SOPs should address investigator-IRB interactions and communications (Klitzman 2015).

Public engagement is important for promoting the public's trust in the research enterprise (Wynne 2006, National Health Research Ethics Committee of Nigeria 2007; Holzer et al. 2014). Many of the public engagement activities described for promoting the community's trust can also promote the public's trust. For example, investigators can provide the public with information about their research via media interviews, blog postings, website development, and other forms of communication. Investigators can learn about the public's needs and concerns by surveying or interviewing members of the public or soliciting public input at open meetings or focus

[6] The Institutional Review Board Researcher Assessment Tool (IRB-ART) is a widely used survey instrument obtaining data on researchers' perceptions of the IRB (Keith-Spiegel and Koocher 2005).

groups (Resnik 2011b). Investigators can also promote public trust by taking steps to ensure that research is conducted per scientific and ethical standards and responding quickly and appropriately when problems arise. Investigators, institutional officials, and government funding agencies should be accountable to the public. For example, investigators should not avoid difficult ethical questions about their research and should be able to publicly defend it (Yarborough 2014). Government officials should also answer questions about research and justify funding decisions. Funding agencies should solicit the advice of the public concerning research priorities and should fund research that the public considers to be socially valuable (Resnik 2009b). Transparency is also important in building the public's trust (National Health Research Ethics Committee of Nigeria 2007). For example, the results of government-funded research, including data and methodologies, should be available to the public. Investigators and institutions should also disclose and manage financial and other conflicts of interest (Kelch 2002). Finally, as discussed in Chap. 2, government agencies and institutions can promote public trust by developing regulations and guidelines pertaining to the ethical oversight of research.

4.6 The Relationship Between Moral Principles and Research Regulations and Guidelines

The four principles discussed in Chap. 3 (i.e. respect for dignity/autonomy, non-maleficence, beneficence, and justice) together with the principle of trust can justify regulations and guidelines for protecting human research subjects. The members of the National Commission who authored the *Belmont Report* were charged with developing ethical principles to provide a conceptual foundation for revisions of the federal research regulations (see discussion in Chap. 2). The four principles described in Chap. 3 are similar to the *Belmont* principles and can function in the same way. I will briefly describe how these five principles justify some common research regulations and guidelines (see Table 4.2). For further discussion and illustration see Emanuel et al. (2000).

As mentioned in Chap. 3, respect for dignity/autonomy justifies informed consent rules, because these rules enable autonomous individuals to decide whether to participate in research. Non-maleficence provides additional justification for these rules because consent allows individuals to avoid participating in studies they judge to be excessively risky (Brock 2008). Informed consent requirements can promote trust by facilitating honest and open communication between investigators and subjects. Adherence to informed consent rules can help prevent the sense of betrayal and loss of trust that subjects may experience if they discover that they have not been fully informed about some key aspect of a study (as occurred in the Gelsinger case, discussed in Chap. 2) or that they have participated in research without giving their permission (as occurred in the Tuskegee study case, also discussed in Chap. 2).

Table 4.2 Relationship between moral principles and ethical/legal requirements

Requirement	Justifying principle(s)
Informed consent	Respect for dignity/autonomy
	Non-maleficence
	Trust
Confidentiality/privacy protection	Respect for dignity/autonomy
	Non-maleficence
	Trust
Risk minimization	Non-maleficence
	Trust
Social value	Beneficence
	Trust
Reasonableness of risks	Non-maleficence
	Beneficence
	Trust
Sound scientific design	Beneficence
	Non-maleficence
Equitable subject selection	Non-maleficence
	Beneficence
	Justice
	Trust
Protection for vulnerable subjects	Respect for dignity/autonomy
	Non-maleficence
	Justice
	Trust
Independent review	Respect for dignity/autonomy
	Non-maleficence
	Beneficence
	Justice
	Trust

Respect for dignity/autonomy, non-maleficence, and trust also justify rules concerning the protection of confidentiality and privacy in research. Rules pertaining to privacy and confidentiality respect autonomy by giving subjects control over the use of their private information.[7] These rules also protect subjects from harm by preventing discrimination, stigma, embarrassment, identity theft, and other adverse consequences from unauthorized disclosure of private information.[8] Confidentiality

[7] Chapter 6 will explore privacy and confidentiality issues in greater depth.

[8] In the U.S., various federal and state laws protect individuals from discrimination in employment and health insurance. Some of these include: the Americans with Disabilities Act, the Civil Rights Act, the Genetic Non-Discrimination Act, and the Health Insurance Portability and Accountability Act (HIPAA). However, these laws do not cover every type of discrimination that could occur, such as discrimination when applying for life insurance or a mortgage, and not all of them have been well-tested by the courts. Thus, discrimination may still occur in the U.S. and other countries, despite laws that prohibit it (Hudson 2007; Hodge and Gostin 2008).

protections can also promote trust by assuring subjects that their private information will be protected from deliberate or inadvertent disclosure. This assurance can make subjects comfortable disclosing private information to investigators that they might not disclose without confidentiality protections.

The principle of non-maleficence justifies the requirement to minimizing risks to research subjects, since minimizing risks helps to prevent causing harm to subjects. The principle of trust also justifies this requirement since subjects reasonably expect that they will be protected from unnecessary harms related to their research participation. Under the category of risk minimization, I include requirements for data and safety monitoring in clinical trial and reporting unanticipated problems, non-compliance, and adverse events to the IRB.

The principles of beneficence and trust justify the requirement that research should be expected to yield valuable results for society. Beneficence justifies this requirement since this principle obligates researchers to conduct research that can promote the welfare of other people. Trust justifies this requirement since research subjects are likely to expect that their participation in research is necessary to obtain socially valuable knowledge (Emanuel et al. 2000; Resnik 2016a, b).

The principles of beneficence, non-maleficence, and trust justify the requirement that risks are reasonable in relation to expected benefits. Risks are reasonable if they are justified in terms of expected benefits to the subjects or society via the knowledge gained. The principles of non-maleficence and benefice play a key role in justifying this requirement, since for risks to be reasonable, risks must be minimized and benefits maximized (Emanuel et al. 2000). Trust also helps to justify this requirement, since minimizing risks and maximizing benefits helps to assure subjects that they are participating in valuable research and not being unnecessarily exposed to risks.

The principles of beneficence, non-maleficence, and trust also justify the requirement that risks research be scientifically sound. If research is poorly designed, it may not yield any useful knowledge, i.e. social benefits. If research is not likely to yield useful knowledge, then the risks many not be reasonable in relation to expected benefits and subjects may be unnecessarily exposed to risks (Emanuel et al. 2000). Trust also plays an important role in justifying this requirement, since subjects are likely to expect that research is well-designed and that their participation is likely to help address important scientific questions.

The principles of non-maleficence, beneficence, justice, and trust justify the requirement that subject selection be equitable. Subject selection is equitable insofar as a study focuses an appropriate class of subjects for addressing a research question (Levine 1988). Risk minimization is related to subject selection, since subjects should be excluded to protect them or others from harm. For example, subjects who are not healthy should be excluded from a Phase I safety studies of new drugs to protect them from harm, and pregnant women may also be excluded from these same studies to protect their fetuses (Levine 1988).[9] Beneficence is also related to

[9] There are four phases of drug trials involving human research subjects. Phase I clinical trials are small studies (typically less than 100 subjects) which enroll healthy individuals and last only a few

subject selection, since choosing the appropriate class of subjects is important for ensuring that the research will yield valuable knowledge. For example, a Phase II study concerning the safety and efficacy of a drug to prostate cancer should include only men with prostate cancer, since including subjects who do not meet this criterion (e.g. women or men without prostate cancer) may compromise the usefulness of the data. Justice plays an important role in subject selection since studies should not unfairly include or exclude certain classes of subjects. For example, it would unfair to include mentally disabled subjects in a study unrelated to their disease or condition (National Commission 1979). It would also be unfair to exclude categories of subjects, such as members from certain racial or ethnic groups, from a study concerning a disease or condition which is prevalent in among members of these groups (Meltzer and Childress 2008). Finally, justice also plays an important role in justifying the requirement that subject selection is equitable since it helps to assure subjects that they be protected from unnecessary harm and that their participation is likely to help produce knowledge useful to people with their disease or condition or society as a whole.

The principles of respect for dignity/autonomy, non-maleficence, justice, and trust justify the requirement to include additional protections for vulnerable subjects in research. A common procedure for protecting vulnerable subjects is to limit the risks they may be exposed to in research which is not likely to benefit them. The rationale for this requirement is that subjects who have a compromised ability to consent should be protected from harm, since they are not able to make sound decisions concerning their exposure to research risks. Subjects who have good decision-making abilities can decide to enroll in risky studies which are not likely to benefit them, such as Phase I drug trials. The principle of respect for dignity/autonomy comes into play when investigators include procedures for assessing the decision-making capacity of vulnerable subjects, such as mentally disabled individuals. If a mentally disabled individual has the capacity to consent to research, then they should be allowed to do so. If not, then a legally authorized representative, such as a guardian, may consent for them. Justice is also an important concern in additional protections for vulnerable subjects, since it would be unfair to include vulnerable subjects in research that is not relevant to their disease or condition. Vulnerable subjects should be included in research only if their inclusion is important for

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months. The primary goals of Phase I studies are to assess drug safety and obtain information on dosing, toxicology, and pharmacokinetics. If a drug makes it past Phase I, the manufacturer can go ahead with a Phase II study. Phase II trials are larger studies (typically around 300 subjects) which enroll individuals with a disease or condition treated by the drug and may last several years. The primary goals of Phase II studies are to assess safety and efficacy. Phase III trials are similar to Phase II studies, except they are much larger (typically around 3000 subjects). Phase IV trials are also large (typically thousands of subjects) and are conducted after the drug has been approved. Phase IV trials also collect data on safety and efficacy and may include classes of subjects not included in earlier studies. For example, if people 60 years or older were excluded from earlier studies to protect them from harm, they might be included in Phase IV trials if they data indicate that it is likely to be safe to include them (Food and Drug Administration 2015).

addressing a scientific question (National Commission 1979). For example, it would be unfair to include patients with moderate dementia in Phase I drug studies, but it might be fair to include them in Phase II studies designed to treat their disease. Finally, the principle of trust can help to justify additional protections for vulnerable subjects, since these safeguards can assure vulnerable individuals and their parents, guardians, or caregivers (as the case may be) that they will not be unfairly included in research.

All five principles justify the requirement for an independent board, such as IRB, to review and oversee research. Investigators have an inherent conflict of interest when it comes to reviewing and overseeing their own research, since they may fail to notice or deliberately overlook problems that may interfere with conducting research (Emanuel et al. 2000). An IRB is in a better position to identify these problems and make recommendations to correct them. IRB review can help to assure that the research meets various ethical and legal requirements, such as risk minimization, sound scientific design, informed consent, protection of confidentiality/privacy, equitable subject selection, etc. IRB review can also promote the trust of research subjects and community members by assuring them that an independent board is reviewing and overseeing research. For review and oversight to be independent, board members must not have any conflicts of interest that could compromise their judgment. For example, an IRB member should not review a study in which he or she has a financial interest. An IRB member should also not review a study he or she is significantly associated with as a principal investigator, associate investigator or collaborators. IRB members who have conflicts of interest should declare them to the board and recuse themselves from discussion and voting on matters in which they are conflicted (Wolf and Zandecki 2007).

4.7 The Role of Trust in Resolving Ethical Dilemmas in Research with Human Subjects

The goal of promoting trust not only provides additional justification for regulations and guidelines that protect human subjects but it also has applications for disputes involving the interpretation of regulations and guidelines or other ethical dilemmas involving competing values or principles. For example, consider the ethical dispute in the SUPPORT study (discussed in Chap. 1) concerning informing the parents about the risks of randomizing their newborns to different blood oxygenation levels (85–89% vs. 91–95%). Much of the debate focused on whether the regulations required the investigators to inform the subjects about the risks of randomization. Those who favored informing the participants asserted that these potential risks could be reasonably anticipated, whereas those opposed to informing them dispute this claim. One way of thinking about the dispute is to ask: how would informing parents about the potential risks of randomization impact their trust in the investigators or institutions? If informing the parents would probably promote trust, then

investigators should do it, according to the view developed here. One reason why informing the parents could have promoted trust is that it could have helped to avoid that sense of betrayal that they might feel if they were to find out after consenting that they were not informed about the risks of randomization, an unfortunate situation which, in fact, happened. Informing the parents could have also promoted honest and open communication between the parents and the investigators concerning the risks of the study, the research design, and the importance of the research. Finally, informing them could have avoided the investigation by the Office and Human Research Protections and the ensuing adverse publicity, which may have negatively impacted the public's trust in this type of research and the scientific enterprise.

In the controversial HIV prevention trials, also discussed in Chap. 1, one could argue that the investigators followed a process designed to promote trust, because they consulted with public health officials and researchers in the host nations in developing the study design (Varmus and Satcher 1997). Local populations did not raise significant concerns about including placebo control groups because they wanted access to an inexpensive, effective treatment as soon as possible to deal with crisis they faced (Mbidde 1998). The ethical critique of the study design came largely from outside medical professionals and bioethicists who had little involvement with the affected populations.

For another example, consider the Facebook study, also discussed in Chap. 1. This study also involved a dispute about the adequacy of informed consent. While some defended the study on the grounds that the user agreement constituted consent for the study, others said that this agreement did not provide adequate consent because it did not include enough information (Goel 2014). Viewing this dispute from the perspective of promoting trust, one can see that the study probably undermined Facebook users' trust in the organization and may have undermined the public's trust in social media research. To avoid breeding distrust, the investigators could have taken additional steps to ensure that Facebook users had more information about the study. For example, they could have notified all Facebook users about the study and allowed them to agree or not agree to participate. To minimize the potential for bias, the investigators could select a random sample of users who agreed to participate for inclusion. That way, the subjects would not know that their behavior was being studied. Although the federal research regulations did not apply to this study because it was conducted by a private organization, one could argue that Facebook should nevertheless have complied with these rules not to meet legal mandates but to promote trust in the organization and in social media research. As it turned out, the episode proved to be embarrassing for Facebook and the investigators (Goel 2014).

In Chaps. 5, 6, 7, 8, 9, 10 and 11, I will apply the principle of trust to a variety of ethical and regulatory disputes in research with human subjects. I hope to show that the goal of promoting trust can provide us with some useful insights for developing rules or guidelines or making decisions in particular cases, even if it cannot solve every problem.

4.8 Objections to My View

Before concluding this chapter, I will consider several objections to my view. Addressing these objections is important for answering potential critics and explaining my view in more detail.

The first objection is that whether a particular strategy, policy, or decision is likely to promote trust is an empirical question best answered by conducting research into the social psychology of trust. The points I make in this book are little more than philosophical speculation unless they are supported by evidence from empirical research on trust. A psychologist or sociologist is better qualified to write a book on trust in research with human subjects than a philosopher.

I agree that a great deal of what I have to say about trust is a based on empirical assumptions concerning effective methods for promoting trust. Some of the claims I make about trust are supported by empirical studies which I have referred to in this book (see, for example, Fukuyama 1995; Kass et al. 1996; Govier 1997; Corbie-Smith et al. 2002). Other claims concerning trust are based on our common knowledge of human relationships. For example, you do not need to conduct an extensive survey of human attitudes and beliefs to understand that lying and deception undermine trust. However, some claims I make are indeed speculative at this point, and more research is need to determine whether they stand up to further scrutiny. For example, I have claimed that community engagement can promote trust in research institutions. While this claim seems highly plausible, more research is needed on the relationship between community engagement and trust in research institutions, and how best to engage communities. I acknowledge the empirical character of much of what I have to say about trust and welcome and encourage additional research on the nature of trust in research involving human subjects.

Additionally, I would like to point out that many of the normative claims in applied ethics depend on empirical claims or assumptions concerning psychology, sociology, or economics. For example, one of the main arguments for the death penalty is that it deters crime (Reiman and Pojman 1998). To evaluate this argument, one needs to obtain empirical evidence concerning the death penalty's impact on decision-making and behavior. In research ethics, one of the main arguments for limiting the amount of money that human subjects can receive for their participation is that excessive financial compensation can compromise informed consent by affecting subjects' judgments concerning risks and benefits. To evaluate this argument, it is necessary to obtain empirical data on the impact that financial incentives have on the decision to participate in research (Resnik 2015b). To develop well-supported arguments and positions which provide guidance for real-world problems, it is often necessary to draw upon and interpret relevant facts and scientific research. Indeed, many bioethicists have urged their peers to conduct empirical research on bioethics topics and to engage the relevant scientific literature to enhance the practical value of bioethical reflection (Kon 2009).

The second objection is that trust approach implies ethical relativism, which is an untenable position (see Chap. 3 for more on this point). The trust approach implies

ethical relativism because what makes someone or something trustworthy can vary a great deal across communities and cultures. For example, in some Islamic and African societies it is customary for a woman's spouse or older male relative, to provide consent for her (Afifi 2007; Princewill et al. 2017). The trust framework I have developed would seem to imply that investigators conducting research in these societies should honor their traditions concerning consent to promote trust. However, one might argue that the obligation to obtain consent from the research participant is a universal ethical requirement that investigators should follow, regardless of the customs, values, or expectations of the local community.

I have a couple of response to this objection. First, I would argue that what makes research trustworthy does not vary across cultures and communities as much as this example suggests. Some values, such as confidentiality, protection from risks, competency, and so on, are widely held across different populations or communities.

Second, I would also point that none of the ethical principles I am defending are absolute: they are *prima facie* rules that may conflict with each other in particular cases. When conflicts arise, we must decide which principle should have priority. I have argued that we can appeal to the goal of promoting trust when dealing with conflicts among the other principles, such as non-maleficence vs. beneficence. We can do the same when trust conflicts with other principles. In the example discussed above, one needs to decide whether it is more important to promote trust by following the community's traditions concerning consent, or to respect the woman's dignity/autonomy by seeking consent from her, not from her spouse or older male relative. To establish priorities in this situation, one could appeal to another principle, such as non-maleficence. One could argue that obtaining consent only from the woman could result in harm to her, since she might face repercussions from her family. A compromise position would be to obtain consent from the woman and ask her whether she would also like her spouse or older male relative to give permission for the research. The woman could designate her spouse or older male relative as the decision-maker, if she so chooses. Following this plan of action would protect the woman from harm, honor the local tradition, and respect the woman's decision-making since she could decide whether to include her family in the decision. The woman would also retain the right refuse to participate in the study. (See Chap. 5 for further discussion of this issue.)

Although I think this is a reasonable response to the second objection, I am mindful of the concerns raised by this objection. To promote trust among investigators, subjects, institutions, and communities it is important to understand local traditions, customs, values, and concerns, so that these can be taken into account when designing research, recruiting subjects, and so forth. Community engagement can help investigators obtain information about the local research context. When honoring local traditions, customs, values, and concerns conflicts with research regulations or moral principles, investigators and IRBs must consider how best to promote trust while adhering to ethical and legal rules. Promoting trust is an important consideration, but not the only consideration, in conducting ethical research with human subjects.

A third objection, which is related to the second one, is that communities may place unreasonable demands on investigators, sponsors, or institutions. One might

argue that investigators and institutions are not obligated to meet unreasonable demands so that they can promote trust. For example, suppose that members of a particular community expect medical researchers to provide subjects with a wide array of free medical and dental care in exchange for their participation. One might argue that this demand is unreasonable, since it would strain the research budget and compel researchers to exceed the scope of their expertise. The sponsor might not have sufficient resources to fund the study.

To answer this objection, we need to ask what it means for subjects or communities to make unreasonable demands. If the demands placed on investigators, sponsors, or institutions would make it practically impossible to conduct a study as a result of resource limitations or other constraints, then these demands would prevent the study from being conducted, which would deny the subjects and community important benefits. In deciding whether—or how—to conduct the study, the investigators, sponsor, and institution would need to balance two competing principles, beneficence and trust. They may be able to find a workable solution in which they provide subjects with some medical care that fits within the research budget even though do not meet all the community's demands (de Melo-Martín and Ho 2008).

A fourth objection is that trust is incompatible with legal oversight. Trust is essentially an ethical, not a legal notion. If we trust someone, we do not need legal rules governing their behavior, and we impose legal rules on people because we do not trust them. As noted in Chap. 2, prior to the development of the federal regulations governing research with human subjects, the trust that subjects placed in the investigators' integrity was paramount (Moreno 2001).

My response to this objection is that trust is compatible with legal oversight. It is possible to trust someone whose behavior is also governed by legal rules. For example, we trust banks to keep our money safe even though many legal rules govern the banking industry. Indeed, one of the reasons why we trust banks is that we know that they have legal obligations to protect our money. During the financial crisis of 2008, the U.S. Congress enacted laws to help secure the public's trust in banks. An independent commission found that lack of adequate banking regulation was a primary cause of the crisis (Chan 2008). Likewise, in Chap. 2 we saw how the U.S. government enacted legal rules pertaining to research with human subjects to promote the public's trust. President Reagan used the phrase "trust but verify" when negotiating arms control treaties with the Soviet Union (Massie 2013). A similar phrase "trust but regulate" applies to research with human subjects.

A fifth objection is that sometimes trust may be misplaced. For example, the participants in the Tuskegee study (discussed in Chap. 2) probably trusted the doctors and medical staff to take good care of them, but their trust was misplaced because the investigators withheld important information from them, i.e. that they were in a research study and that a treatment for syphilis had become available. Thus, we would not say that trust should be promoted in this case because it was based on deception.[10]

In response to this objection, I would say that trust involves the expectation that the people you are trusting are behaving ethically. When trust is misplaced, the

[10] Henry Richardson pointed out this objection.

entrusted parties are not behaving ethically. Thus, the goal of promoting trust should include the proviso that trust is properly founded on expectations of ethical conduct.

A final objection is that trust is not unique to research with human subjects, since it is also an important concern in medicine, government, business, and many other professions or endeavors. Hence, what I have to say about trust in research with human subjects is not particular original or noteworthy.

I'm not sure this is really an objection to my view but more of an observation. I agree that much of what I have to say about trust in research with human subjects applies to other professions or endeavors. I could envision someone developing a trust-based approach to medical or government ethics, for example. However, I think there are some important differences between research with human subjects and other activities where trust is also paramount. First, investigators and research institutions often have interests which are contrary to the interests of research subjects and communities. Investigators and institutions are interested in obtaining knowledge, whereas subjects and communities are mostly interested in deriving benefits from research participation and having their rights protected (Miller and Brody 2002, Merritt 2005). Investigators and institutions may also have significant financial interests related to research (Resnik 2007a). Because the interests of investigators, institutions, subjects, and communities do not always coincide, trust can become an important issue, since stakeholders in these relationships may be concerned the other stakeholders will act in ways that compromise their interests. For example, research subjects may be concerned that investigators' interests in obtaining knowledge will prevent the investigators from taking appropriate steps to protect subjects from harm. In contrast, investigators may be concerned that research subjects will not disclose information truthfully during enrollment because they are interested in receiving money for participation. Second, as documented in Chap. 2, the history of research with human subjects unfortunately includes many instances involving the betrayal of trust. Investigators and institutions have betrayed the trust of subjects, communities, and the public; investigators have betrayed each other's trust; and so on. Regulations and ethical guidelines have been adopted, in large part, to restore and maintain trust. For these two reasons, trust is especially important in research with human subjects, perhaps even more so than in other human activities.

4.9 Conclusion

In this chapter I have argued that the goal of promoting trust serves as a principle for conducting ethical research with human subjects. I have explored the nature of trust in research with human subjects, discussed some strategies for promoting trust, considered some alternatives approaches to trust, and addressed objections to my view. The principle of trust complements four other moral principles developed by Beauchamp and Childress (2012), i.e. respect for dignity/autonomy, non-maleficence,

beneficence, and justice. One can appeal to these five principles to justify research regulations and guidelines to make decisions in particular cases. The principles are not absolute requirements, but *prima facie* rules which may conflict in some situations. When conflicts arise, one can consider the relevant facts and options to decide which one should take priority. We can use the principle of trust to resolve conflicts among the other four principles, but the principle of trust is not a meta-rule for decision-making. That is, the goal of promoting trust may sometimes conflict with the other principles, and we must decide whether it is more important to promote trust or to honor these other principles. In Chaps. 5, 6, 7, 8, 9, 10 and 11 I will apply my trust-based approach to a variety of topics in the ethics of research with human subjects.

Chapter 5
Informed Consent

In the first four chapters of this book, I examined the historical and philosophical foundations of the ethics of research with human subjects and developed a theoretical framework for decision-making. The key insight of this framework is that promoting trust is an important principle for making ethical decisions concerning research with human subjects. In the book's remaining eight chapters I will apply my framework to various topics in human research ethics and discuss its implications for practice and policy. The first topic I will address is informed consent, since trust and consent are closely connected.

5.1 Trust and Informed Consent

As argued in Chap. 4, informed consent is important for promoting trust between subjects and investigators, because it helps to assure subjects that investigators will treat them with respect and protect them from harm. During the consent process investigators describe not only their research goals, methods, and procedures but also measures they will take to protect subjects' rights and welfare. Consent is a kind of mutual agreement between investigators and subjects in which both parties affirm their intentions to behave in particular ways (Faden et al. 1986). The consent form provides a written record of this agreement, but the process of consent includes much more than reading and signing a form and encompasses other types of communication between investigators and subjects, such as advertisements, brochures, reminder emails and letters, newsletters, informal conversations, and so on (Faden et al. 1986). To help solidify trust, investigators should communicate honestly and openly with subjects during the consent process (Sanchini et al. 2016).

Not only is consent important for promoting trust, but it also presumes a certain amount of trust. Consent documents often contain medical, scientific, or legal jargon and have an average length of 10 or more single-spaced typed pages (Resnik

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et al. 2008). One study found that the average consent form is written at the 10th grade reading level, even though ethical guidance states that forms should be written at an 8th grade level or lower (Paasche-Orlow et al. 2003). Because consent forms can be difficult to read and comprehend, subjects often rely on investigators (or research staff) to help them understand important information contained in these documents (Berg et al. 2001; Albala et al. 2010). Investigators can translate technical terms into lay-language, explain complex concepts, and address subjects' questions. For these oral communications to be meaningful, subjects must trust that investigators will not to hide or obfuscate important information (Menikoff 2006). One of the key problems with the informed consent process in the Gelsinger case (discussed in Chap. 2) is that the investigator and his staff members did not clearly explain the risks of the research or their financial interests to the research subject.

5.2 The Elements of Consent

Legal theorists and ethicist have developed five different necessary conditions (or elements) for consent to be valid (Faden et al. 1986):

Competence In the law, competence refers to the legal capacity to make a decision. Adults are presumed to be competent unless they have been adjudicated incompetent by a court. When a court declares someone to be incompetent it will appoint a guardian to make decisions for that person (i.e. the ward). A court may grant a guardian full authority to make decisions for the ward, or it may limit the guardian's authority to making medical or financial decisions. Children are legally incompetent unless they have been emancipated by a court. A judge may emancipate a minor if he or she determines that the minor is economically independent and emancipation is in the minor's best interests (e.g. emancipation is necessary to prevent parental abuse). Marriage automatically emancipates minors in some U.S. states. The age of adulthood is 18 in most states (Berg et al. 2001).

Competence is not the same as decision-making capacity (DMC), which is an ethical and clinical concept. A person has DMC if they are capable of making a responsible choice, i.e. they are autonomous. A mentally ill or disabled adult could be legally competent but lack DMC, and an intelligent 17-year-old might have DMC but not be legally competent. Unlike competence, DMC comes in degrees (Buchanan and Brock 1990). For example, a person who is fully awake and alert may have near perfect DMC, but someone who is tired or ill may have compromised DMC. The degree of DMC required to make a decision is a function of the choice's complexity and level of risk. For a simple, low-risk choice, such as ordering a meal, a low degree of DMC may be sufficient, but for a complex, high-risk choice, such as deciding whether to accept life-saving medical care, a high degree of DMC would be required. To establish the degree of DMC needed to make a decision one must balance two competing ethical considerations: the obligation to respect the person's autonomy and the obligation to protect the person from harm. Factors that

can impact DMC include: age (or maturity), mental illness or disability, emotional distress, and drugs. DMC can also be context-dependent. For example, a mentally disabled adult may be capable of painting homes but unable to manage his or her money (Buchanan and Brock 1990).

The federal research regulations address the issue of competence by stating that consent must be obtained from the subject or the subject's legally authorized representative (Department of Health and Humans Services 2009, 45 CFR 46.116). The regulations also include additional protections for children (45 CFR 46, Subpart D).

Information The person providing consent must have enough information to make a responsible choice. As noted in Chap. 2, the federal research regulations specify some types of information that investigators must disclose to subjects during consent (45 CFR 46.116). I will discuss in the disclosure of information at greater length in the Disclosure Standards section (below).

Voluntariness The person providing consent must be able to make a free choice. The federal research regulations state that consent should take place under circumstances that "minimize the possibility of coercion or undue influence (45 CFR 46.116)." Coercion involves the use of force, intimidation, or threats to make someone comply with a demand or request. A threat could involve the prospect of physical, psychological, or economic harm, including the loss of a benefit that one is entitled to (Wertheimer and Miller 2008). For example, if a professor made participation in his experiment a requirement for one of his courses, this would be coercion, since students who refused to participate could suffer a grade penalty. Undue inducement is exerting inappropriate influence over someone's decision-making to cause them to make a particular choice. For example, if a professor seeks to have sex with one of her students, this would be undue influence because the professor's position of power over the student would inappropriately influence the student's decision to engage in sexual activity (Resnik 2015b). I will discuss coercion and undue influence in greater depth in the Consent by Parties other than the Subject, Right to Withdraw, Payment for Research Participation sections (below) and in Chap. 9, which deals with vulnerable subjects.

Comprehension The person providing consent must be able to comprehend or understand the information. The federal research regulations have very little to say about comprehension other than to state that information presented to the subject or representative must be in "language understandable to the subject or representative (45 CFR 46.116." This phrase is usually interpreted as implying: (1) that consent shall take place in a language that the subject or representation is capable of understanding (e.g. if the subject only speaks Spanish, then the consent form should be written in Spanish and someone who speaks Spanish should conduct the consent); (2) technical terms from science, medicine, or law should be interpreted into lay-language (Berg et al. 2001). The revisions to the Common Rule include the requirement that "The information must be presented in sufficient detail relating to the specific research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's

or representative's understanding of the reasons why one might or might not want to participate (Department of Homeland Security et al. 2017, 45 CFR 46.116)."

Numerous studies have shown that research subjects often have difficulty understanding information disclosed during consent (Flory and Emanuel 2004). Subjects in clinical research often succumb to a misunderstanding, known as the therapeutic misconception, when they mistakenly believe that the primary goal of a study is to provide them with treatment rather than to gain scientific knowledge (Henderson et al. 2007; Lidz et al. 2015). Subjects who do not understand that the primary goal of a study is to develop scientific knowledge may overemphasize the expected benefits from participating in the study. They may also fail to understand that they will be randomized to different treatment groups or that they may receive a placebo (Appelbaum and Lidz 2008). As a result, they may decide to participate in research without carefully considering the benefits, risks, and alternatives. The federal research regulations require investigators to inform subjects that the study they are participating in involves research (45 CFR 116a1). However, many subjects fail to appreciate the difference between research and therapy even when they are told that they are participating in research (Appelbaum and Lidz 2008).

Appelbaum and colleagues described the therapeutic misconception 30 years ago, and numerous studies have documented the phenomenon since then (Appelbaum et al. 1982, 1987). This misunderstanding continues to persist even though clinical investigators have known for many years that they should try their best to dispel it (Appelbaum and Lidz 2008). There are several possible explanations for why clinical research subjects often fail to appreciate the difference between research and therapy. First, subjects who a seriously ill may cling to whatever hope they have of finding a cure and doctors may be hesitant to undercut their hope, because they know that hope can be a powerful healing force in medicine. Hope may lead subjects to mistakenly believe that studies they are participating in have been designed to cure them. When a doctor tells them that "the goal of this study is develop new knowledge, and you may not benefit from participating in it" they may believe that they will benefit (Appelbaum et al. 1987). Second, subjects expect doctors to provide them with medical treatment, and it can be difficult for subjects who have been treated by doctors for many years to start thinking of them as scientific researchers. They may have a difficult time making the mental leap from therapy to research. Third, subjects may trust that their doctors will always act in their best interests. Some patients have so much trust in their doctors that they will agree to participate in a clinical trial before reading the consent form (de Melo-Martín and Ho 2008).

Because the therapeutic misconception can compromise informed consent, clinical investigators should carefully explain the difference between research and therapy, and identify procedures done for research purposes and experimental treatments. They should also help their patients understand the risks and benefits of the research and forms of treatment which may be available outside of the study (Menikoff 2006; Appelbaum and Lidz 2008). Clinical investigators can help their patients avoid the therapeutic misconception without taking away their hope or betraying their trust.

Authorization The person providing consent must agree to the interaction that requires consent, such as participating in research or receiving medical care. The person may communicate their agreement verbally, by signing a document, or by making some other sign of authorization (e.g. nodding their head).

5.3 Disclosure Standards

Although the federal research regulations (Department of Health and Humans Services 2009, 45 CFR 46.116) specify some types of information that must be disclosed to subjects during consent, they do not cover every possible type of information that could be disclosed.[1] For example, the regulations do not state whether conflicts of interest or sources of funding must disclosed to research subjects (Resnik 2004). The regulations are also subject to interpretation, as we saw in the SUPPORT study (discussed in Chap. 1). Thus, there are still important ethical issues concerning disclosure standards for research involving human subjects (Menikoff 2006; Manson and O'Neill 2007). Investigators and IRBs often face two basic ethical questions concerning disclosure: (a) what kinds of information should be disclosed?; and (b) how much information should be disclosed? The SUPPORT study involved an ethical dispute concerning question of type (a). For a potential example of a question of type (b), imagine that an investigator is trying to decide whether to disclose information concerning rare risks associated with a study medication. This question would be about not whether to disclose medication risks but how many risks to disclose.

Legal decisions, articles, and books mention three different standards for disclosing information (Faden et al. 1986; Berg et al. 2001; Menikoff 2006). The first is the professional standard: an investigator should disclose the information that a reasonable member of the profession would disclose. The second is the reasonable person standard: an investigator should disclose the information that a reasonable person would want to know. The third is the subjective standard: an investigator should disclose the information that this particular subject would want to know (Faden et al. 1986).[2] 25 U.S. states use the professional standard, 23 use the reasonable patient standard, and 2 use the subjective standard (King and Moulton 2006).

Commentators have criticized the professional standard on the grounds that it may compromise the subject's autonomy, since professional norms for information disclosure often emphasize non-maleficence and beneficence over autonomy (Faden et al. 1986; Berg et al. 2001). For example, oncologists often perform clinical trials comparing the effectiveness of different cancer treatments (or combinations of

[1] Chapter 11 will disclose additional disclosure requirements in the revision to the Common Rule.

[2] The shared decision-making approach to medical choices can viewed using a subjective standard for information disclosure because a shared decision is one in which the physician and patient both work together to share information relevant to the decision. This approach is subjective because what is relevant to the decision is determined, in part, by the patient's preferences and values. See Charles et al. (1997), Whitney et al. (2004).

treatments) which have been approved for marketing. One study found that only 17.4% of oncology consent forms disclosed the availability of treatment off-study (Resnik et al. 2008). Clinical researchers have argued against disclosing this information to research subjects on the grounds that it would not be in their best interests to receive the treatment off-study, since it might be dangerous to take the treatment without the careful monitoring that occurs in a clinical trial. Critics of this practice have argued, however, that most patients would want to know whether they can receive a treatment without participating in a study (Menikoff 2006). Another problem with the professional standard is that members of the profession may disagree about what should be disclosed. If members of the profession are more or less evenly divided concerning disclosure issues, it may be difficult to determine what a reasonable member of the profession would disclose.

While the subjective standard respects autonomy, commentators have criticized it on the grounds that it places unreasonable demands on investigators, since it compels them to find out what a particular subject would want to know (Berg et al. 2001; Manson and O'Neill 2007). To accomplish this task, one might need to engage in an extensive dialogue with prospective research participants to learn about their values, interests, goals, and background knowledge. For example, suppose that an 18-year-old male is considering volunteering for a study of fat metabolism that involves a muscle biopsy. The informed consent document discusses the risks of infection from the biopsy but has little to say about the resulting scar. The prospective research subject would like to know more about the biopsy scar because he is considering a career in modeling. To obtain this information the investigator (or research staff) would need to find out more this person's career plans. Investigators might not have enough time to ask these sorts of questions, and even if they do, it might not occur to them to ask them. Adopting the subjective standard as a matter of law could open investigators to lawsuits from subjects who decide, after the fact, that they would not have participated in a study had they known some idiosyncratic piece of information (King and Moulton 2006).

Given the problems with the other two standards, the reasonable person standard has emerged as the most popular approach to disclosing information in biomedical research and clinical practice (Faden et al. 1986; Berg et al. 2001). The revisions to the Common Rule, for example, include a requirement that investigators provide subjects with information that a reasonable person would want to know to make a decision concerning research participation (Department of Homeland Security et al. 2017, 45 CFR 46.116). However, the reasonable person standard also has some shortcomings. First, there are some problems with defining the concept of a reasonable person. There are two approaches to understanding the concept of a reasonable person (Miller and Perry 2012). According to the descriptive approach, the reasonable person is the statistically normal (or average) person within a population. Specifying the relevant population poses a significant problem for the descriptive approach, since the statistical norms concerning informational needs and background knowledge may vary considerably across populations. For example, the average person living in a tribe in Nigeria may not be as familiar with the concept of randomization as the average person living in Boston, MA. Therefore, a discussion of randomization in a clinical trial developed for a resident of Boston, MA may

not be appropriate for a member of a Nigerian tribal community. According to the normative approach, the reasonable person is a hypothetical individual who makes appropriate judgments concerning the evaluation of benefits and risks. Determining what makes a judgment "appropriate" is a key problem with the normative approach, since "appropriateness" is a normative concept that is based on prior acceptance of some moral theory, but, as we saw in Chap. 3, there is considerable disagreement about moral theories.

Second, one might argue that the reasonable person standard does not respect autonomy enough because it does not give sufficient attention to the disclosure of individualized information during consent. One might concede that the subjective approach places excessive demands on investigators yet support the idea that investigators should sometimes go beyond the reasonable person standard and disclose information of special importance to particular subjects. For example, one might argue that whenever a research procedure is likely to leave a noticeable scar, investigators should ask subjects whether they have any special concerns about scarring. Although the reasonable person might not require this information to make a decision, some people might need it. Likewise, if investigators are taking blood samples from a community with special beliefs concerning the use, storage, and disposal of blood, they should take these beliefs into account when sharing information with subjects concerning the handling of blood samples. Again, the reasonable person might not need this additional information, but members of this community would need it. If the investigators from ASU had been more aware of the Havasupai tribe's concerns about blood samples they might have been able to avoid the unfortunate misunderstanding that led to a lawsuit (see Chap. 2).

The goal of promoting trust can provide some useful guidance for the disclosure standards used in informed consent. According to principle of trust defended in Chap. 4, disclosure standards should promote trust between the relevant parties, i.e. subjects, investigators, communities/populations, and institutions. The principle implies that investigators should tailor disclosures to the needs of subjects, communities, or populations, because fulfilment of these needs is likely to impact trust. Investigators should attempt to avoid the sense of betrayal which may occur when research subjects discover that they did not receive some relevant information during recruitment and enrollment. For example, if it likely that some subjects may be concerned about the appearance of a scar from a procedure, then investigators should discuss scarring in detail or ask subjects whether they are concerned about it. If it is likely that members of community have special concerns about the handling of blood samples, then investigators should share information designed to address these concerns during consent.

Thus, the principle of trust recommends disclosure standards that tend toward the subjective approach. So why not simply adopt the subjective approach on the grounds that it promotes trust and respects autonomy? The principle of beneficence provides us with a reason to resist the subjective approach, since using the subjective approach could place excessive demands on investigators which strain budgets and compromise their ability to conduct beneficial research. Investigators should attempt to address subject-specific and community or population-specific informational needs to the extent that their efforts to promote trust in this manner do not compro-

mise their ability to conduct beneficial research. Investigators can learn more about subject-specific informational needs during informed consents, and they can learn about community or population-specific needs through community engagement (discussed in Chap. 4). While investigators and staff should allocate sufficient time to the consent process to address subject-specific needs, they should not spend so much time on consent that they do not have enough time left for other research activities. Likewise, budgetary and resource constraints could place limits on community engagement activities. In sum, disclosure standards in informed consent in research with human subjects should carefully balance three principles: respect for dignity/autonomy, beneficence, and trust.

Before concluding this section, it will be useful to say a few words about the amount of information disclosed. Informed consent documents have steadily increased in length over the years (Menikoff 2006). This trend is probably due to several factors, including the increasing complexity of research, greater attention to the informational needs and concerns of human subjects, and pressures to protect the institution from legal liability.[3] Providing more information to a subject may not always improve the consent process. In fact, there is evidence that too much information can undermine consent since the recipient may not be able to understand and process the information. Some ethicists and investigators have recommended shortening and reorganizing the consent document to improve the subject's understanding of the research. For example, a consent document could consist of a 1–2 page summary of the most important information, with the rest of the information available in an appendix or brochure (Flory and Emanuel 2004). Although there is some evidence which suggests that shortening and reorganizing consents documents can improve subjects' comprehension of the material (Flory and Emanuel 2004), investigators and IRBs should approach this strategy with caution, since shortening the form may result in the removal of key information and participants may only read the 1–2 page summary and not pay attention to the supplemental information. The trust approach makes no specific recommendations concerning the amount of information that is disclosed but it would encourage investigators to experiment with different methods of disclosing information, with an eye toward promoting trust.

5.4 Documentation

The federal research regulations require that consent be documented by means of an IRB-approved form which is signed by the subject or the subject's representative (45 CFR 46.117a). The consent form may be a document that includes all the

[3] Consent can reduce or prevent liability for negligence, battery, fraud, conversion, and other torts. For example, battery is commonly defined as unconsented or unwanted touching that causes harm. If someone consents to being touched, they cannot sue for battery. Assumption of risk is a legal defense to a negligence lawsuit. If you inform someone about a risk and they agree to participate in the activity, they have assumed the risk. See Berg et al. (2001).

required information (i.e. the long form) or a short stating that the required information has been presented orally to the subject (or the subject's representative). When the shorter method is used, the subject shall also receive a written summary of the long form and an oral presentation of the long form, which could be a translation into the subject's preferred language. A witness to the oral presentation must sign the short form and the summary. The subject or representative shall receive a copy of the short form and summary (45 CFR 46.117b). The purpose of using the short form is to accommodate subjects who are illiterate, blind, or are not fluent in the language used in research (e.g. English). If researchers expect to enroll subjects from a particular linguistic group (e.g. Spanish) they should translate the long form into their language.

The federal regulations allow the IRB to waive documentation requirements when (1) the consent document is the only written record linking the subject to the research and the only risk of the research is breach of confidentiality, or (2) the research is no more than minimal risk and does not include any procedures for which consent is usually required outside or research participation (45 CFR 46.117c). The revisions to the Common Rule state that documentation can also be waived when risks are minimal and subjects belong to a community or cultural group in which signing a form is not the norm (Department of Homeland Security et al. 2017).

Documentation of consent can help to show respect for the subject's autonomy and promote trust, because the subject may want to have a written record that includes information about research procedures and methods, risks, benefits, confidentiality protections, and so on. Subjects who forget important information can refer to the consent document. It is especially useful for subjects to have a written record of whom to contact if they are injured in the study, have a question about the research, or want to withdraw (Resnik 2009c).

Documentation of consent may undermine trust in some situations, however. For example, if research is conducted in a community in which most people are illiterate and prefer oral communication, use of a written form to document consent may generate suspicion and undermine the community's trust (Onvomaha et al. 2006). In some cultures, people may distrust written documents or see no need for them (Rashad et al. 2004). In some cases, the informed consent document may be misleading or confusing due to difficulties with translating the document into the local written language (Onvomaha et al. 2006). Investigators should use culturally appropriate methods for documenting consent (Council for the International Organizations of Medical Sciences 2002, 2016; Liamputtong 2008). In some cases, no documentation may be the best strategy; in others, use of the short form may be appropriate. Community engagement can help investigators learn about culturally appropriate methods of documenting consent (Seibert et al. 2002). The principle of trust would support a method of documentation that is most likely to promote the subject's, community's, or population's trust.

5.5 Consent by Parties Other than the Subject

As noted in Chap. 2, research regulations and guidelines require investigators to obtain consent from the subject or from the subject's legal representative if the subject is not capable of providing consent, due to immaturity or mental disability or illness (Berg et al. 2001). However, in some communities or societies it is customary for someone other than the research subject to provide consent, even when the subject is capable of consenting. As mentioned in Chap. 4, in some Islamic and African cultures it is customary for a woman's spouse or older male relative to provide consent for medical procedures (Rashad et al. 2004; Afifi 2007; Princewill et al. 2017). Family involvement in the consent process is also common among Latino populations in the Americas (Macklin 1999). In some African societies it is customary for tribal leaders to provide consent for members of the tribe (Onvomaha et al. 2006; Liamputtong 2008). While it is important for investigators to be sensitive to cultural traditions concerning consent (Seibert et al. 2002), allowing someone other than the competent, adult subject to provide consent contravenes research regulations and guidelines adopted by the U.S. and other nations, which emphasize protection individual rights.

Consent by someone other than the competent, adult research subject raises at least two ethical concerns. The first is coercion: consenters might pressure prospective subjects to participate in research against their wishes or better judgment. Coercion could be explicit, e.g. the prospective subject faces a threat from the consenter, or implicit, e.g. the prospective subject complies with the decision of the consenter because he or she wants to please the consenter or avoid making him or her angry. Conversely, the consenter might refuse to allow the prospective subject to participate in research, which could deny potential benefits to the prospective subject, such as participation in a clinical trial. Even if the prospective subject is not likely to derive medical benefits from participation, he or she might want to contribute to advancing the goals of the study. The second concern is privacy/confidentiality: the consenter might learn about private information disclosed during the enrollment process that the subject does not want to share with other people. For example, during the enrollment process, the investigators might ask subjects about drug or alcohol use, sexual abuse, trauma, sexually transmitted diseases, and so on. Even if the consenter is not involved in the enrollment process, he or she would learn that the subject is participating in the study, which could also compromise the subject's privacy or confidentiality. For example, if the study is interviewing women who have a particular sexually transmitted disease, the consenter would learn that the subject has this disease.

Given the concerns about coercion and privacy/confidentiality, there are strong moral reasons for not allowing anyone besides the prospective subject, who is a competent adult, to provide consent for research participation. The principles of respect for dignity/autonomy and beneficence would recommend that no one else besides the subject provides consent. However, prohibiting outside parties from participating in the consent process might undermine the trust of the community and prospective research subjects. Also, as noted in Chap. 4, prohibiting outside parties from being involved in the consent process may result in harm to the subjects. For example, a husband might retaliate against his wife for enrolling in a study without

his permission, or tribal leaders might punish members of the tribe who enroll in a study without their authorization.

One way of dealing with this ethical dilemma is to develop a compromise solution that respects cultural traditions and the prospective subject's autonomy. In Chap. 4 I argued that women's consent for research participation in some Islamic cultures could be obtained by (a) asking the women to consent for research, (b) asking her if she also wants her spouse or older male relative to give permission, and (c) allowing the woman to designate her spouse or older male relative as the decision-maker, if she so chooses. All I would add to these recommendations is that to protect the woman's privacy and confidentiality, investigators should not include the spouse or male relative in the enrollment process, unless she asks that he be included. Investigators should also not inform the spouse or older male relative that the woman is participating in research if she does not want them to know.

For the situation in which consent is traditionally given by tribal leaders, I recommend that investigators consult with the leaders about the research and obtain their approval to recruit members of the tribe but not ask them to provide consent for specific participants (Weijer and Emanuel 2000; Dickert and Sugarman 2005). Members of the tribe would still be free to decide whether to participate in the study (Juengst 1998b). To protect their privacy and confidentiality, tribal leaders would not be told who is or is not participating in the study. Onvomaha and colleagues implemented this type of methodology in conducting research in a tribal community in Northern Ghana (Onvomaha et al. 2006). The investigators consulted with tribal leaders and obtained their permission before recruiting research subjects.

These compromise solutions may not satisfy everyone. For example, husbands or male relatives in Islamic cultures may want to provide consent for their wives or female relatives, not just grant their permission once the woman has already consented. If a woman decides to participate in a study and does not want her husband or older male relative to know about it, she could face repercussions if they find out. Likewise, tribal leaders might want to provide consent for tribal members, not just grant researchers permission to enroll members of the tribe in the study. Human rights advocates may object that these solutions to do not do enough to respect autonomy. A human rights advocate might argue that husbands or older male relatives should have no involvement in a woman's decision to participate in research, even if she asks them to be included. The fact that a compromise does not satisfy all parties is by no means a reason to reject it, since compromises involve some give-and-take. Unless we say that a particular moral principle must always trump other principles, then most of our answers to ethical dilemmas will be compromise solutions.

5.6 Research Without Consent

Although informed consent is one of the most important principles for ethical research with human subjects, one might argue that sometimes it is acceptable to conduct research on human subjects without their consent (Gelinas et al. 2016). As noted in Chap. 2, the Common Rule allows an IRB to waive consent requirements for

minimal risk research that could not be conducted without a waiver. For example, an investigator might ask for a waiver to conduct a study involving the review and analysis of medical records from patients at a hospital on the grounds that the research is minimal risk and it would be too difficult to contact patients to ask them for permission to access their medical records (Miller 2008a).[4] An investigator also might ask for a waiver to conduct a minimal risk hospital quality assurance (QA) or quality improvement (QI) study because the research could not be conducted if consent must be obtained from each patient (see discussion of the JHU QI project in Chap. 1) (Gelinas et al. 2016).[5] The Common Rule also permits investigators to conduct research on de-identified human biological samples (e.g. tissue, blood, etc.) left over from medical procedures or tests without consent (Bathe and McGuire 2009).[6]

The FDA regulations allow IRBs to waive informed consent requirements for conducting research when (1) the patients/subject is facing a life threatening situation that requires a medical intervention; (2) available treatments are unproven or unsatisfactory; (3) the research has the prospect of providing direct medical benefits to the patient/subject; (4) the research cannot be conducted without a waiver of informed consent because the patient/subject is unable to consent and his or her legal representative is not reasonably available. The FDA regulations also require the investigators to publicize the research and consult with representatives of the community prior to implementing study and enrolling participants. Patients should be informed that they are participating in research if they regain decision-making capacity (Food and Drug Administration 2010).[7]

These four types of research without consent described above, i.e. medical records research, QA/QI research, research on biological samples, and emergency research, raise various ethical issues. Concerning research on medical records, one might argue that this violates the subject's autonomy and privacy by interfering with his or her right to control access to his or her medical information. Although allowing investigators to have access to this information poses no risks to subjects if confidentiality protections are in place, subjects may still want to limit access to this information (Miller 2008a). One might respond to this argument by claiming that many people in health care institutions already have access to medical records and that allowing one more person to review them to conduct important research is not a significant invasion of privacy or loss of autonomy (Miller 2008a). For example, hospitals routinely review medical records to obtain data on the utilization of resources or for QA/QI studies. Accessing medical records for research purposes is

[4] The privacy rule of the Health Insurance Portability and Privacy Act (HIPAA) allows an IRB or privacy board to approve research involving review of medical records (National Institutes of Health 2004).

[5] The proposed revisions to the Common Rule exclude internal quality improvement and quality assurance projects from being classified at research (Department of Homeland Security et al. 2015).

[6] Chapter 11 will discuss how the revised Common Rule deals with research involving de-identified biological samples and data.

[7] The Common Rule does not include any provisions for emergency medical research.

not significantly different from performing these other institutional functions, one might argue. Moreover, requiring investigators to obtain consent would prevent them from conducting research that is likely to benefit society. Patients' rights to autonomy and privacy can be restricted to conduct valuable research one might argue (Miller 2008a).

Concerning QA/QI research, one might argue that this violates the subject's autonomy by exposing him or her to potentially risky interventions without consent. If hospital patients should not participate in clinical trials of new drugs without consent, they should also not participate in QA/QI experiments without consent. In response to this argument, one could point out that hospitals already conduct many types of low-risk QA/QI projects without consent. For example, a hospital might attempt to determine whether a color-coding of drug containers helps to reduce medication errors. The only difference between these routine QA/QI activities and QA/QI research projects is that research projects are classified as research because they seek to obtain generalizable knowledge. There is no significant difference in risk exposure (Kass et al. 2013). Moreover, QA/QI research can also benefit society by helping hospitals improve the quality of care (Gelinas et al. 2016). Patients' rights to autonomy can be restricted in order to conduct valuable QA/QI research projects, one might argue (Kass et al. 2013; Gelinas et al. 2016).

Concerning research on leftover biological samples from medical procedures or tests without consent, one might argue that this research violates the patient's right to autonomy by preventing him or her from controlling the use of his or her biological samples. Patients should have the right to decide who has access to their biological samples, even if the risks of research are virtually nonexistent because confidentiality is protected (Bathe and McGuire 2009). Although most patients may not care whether investigators use their leftover biological samples to conduct research, some may. The Havasupai case (discussed in Chap. 2) illustrates the importance that some individuals or communities may place on controlling access to their biological samples. Some individuals or communities may not want their samples used for specific research purposes, regardless of the level of risk associated with the research. They may regard their biological samples as their property. Moreover, research on de-identified biological samples may threaten patients' privacy and confidentiality if investigators attempt to re-identify individuals (Bathe and McGuire 2009).

One might respond to these arguments by claiming that patients do not have legitimate interests in how their leftover de-identified biological samples are used, because they relinquished those interests when they allowed them to be treated as medical waste. A leftover biological sample is no longer your property; it is like an old lamp that you have discarded: when the lamp is in your possession, you have a right to control it, but you give up this right once you throw it away and someone else may claim the lamp. Moreover, investigators can protect patients' privacy and confidentiality by agreeing not to re-identify them. Research should be conducted only on de-identified samples (Bathe and McGuire 2009). Leftover biological samples constitute a rich resource of research material, and it would be a shame to allow this resource to go to waste by always requiring investigators to

obtain consent for the use of this material. One might argue that leftover biological samples can be used in research without consent if the risks to the subjects are minimal and it would be difficult or impossible to contact them to obtain their consent (Bathe and McGuire 2009).

Concerning research without consent during medical emergencies, one might argue that this type of research is unethical because it violates the patient's autonomy by preventing him or her from deciding whether he or she will participate in an experiment (Karlawish 2008). Patients should participate in emergency research only if they consent to it before they lose the ability to make a choice, or if their legal representative consents for them. Informing patients (or their representatives) after the fact that they are participating in research does not respect their autonomy. One could reply to this argument by claiming that autonomy is not an overriding consideration when a person is incapable of making a choice. The well-established emergency exception to informed consent in medicine allows physicians to administer lifesaving treatment without consent when the patient is unable to consent and their legal representative is not reasonably available. For example, if the victim of an automobile accident is unconscious and requires emergency medical treatment, paramedics, nurses, and other medical professionals may administer treatment to the patient to save his or her life. The rationale for this exception is that receiving medical treatment is in the patient's best interests (Berg et al. 2001). However, one might argue that the emergency exemption does not apply in the research setting because participation in research may not be in the patient's best interests. It may be in the patient's best interests to receive the standard emergency care rather than experimental treatment (Karlawish 2008). A proponent of emergency research could reply that sometimes it is in the patient's best interests to participate in an experiment because the experimental treatment is likely to be more beneficial to the patient than the standard care, if any is available. For example, suppose that a patient is bleeding to death and the emergency responders do not have any units of blood that match his rare blood type. They could try to stabilize the patient by giving him a saline solution intravenously, but it might be in his best interests to receive a synthetic blood product that has the capacity to carry oxygen (Dickert and Sugarman 2007).

A second important ethical issue related to emergency research concerns the composition of the study population. An emergency research protocol might enroll a disproportionate number of subjects who are members of socioeconomically disadvantaged groups. There are several reasons why such skewing of the study population might occur. First, members of socioeconomically disadvantaged groups may be more likely to need emergency medical treatment than members of other groups, due to higher rates of violence, gunshot wounds, etc. Second, due to higher rates of homelessness and lower rates of marriage, members of socioeconomically disadvantaged groups may be less likely than members of other groups to have legal representatives available who could refuse research participation on their behalf. Third, it might be the case that the institution conducting the research is a public hospital or medical center which serves a predominantly socioeconomically disadvantaged population. Enrolling a disproportionate percentage of members of socio-

economically disadvantaged groups in a study raises issues of justice, since members of these groups might bear an unfair share of the burdens of research, and justice requires that the benefits and burdens be distributed fairly. An emergency research protocol should therefore include recruitment methods designed to obtain a fair representation of members of different socioeconomic groups (Levine 2008).

A third issue is that the FDA regulations provide little guidance concerning publicity or community consultation (Karlawish 2008). In response to the lack of guidance provided by the regulations concerning community consultation and other issues, the FDA issued some interpretative guidance for investigators, sponsors, and IRBs concerning emergency research (Food and Drug Administration 2013). Community consultation, according to the guidance, serves several goals. Community consultation (1) informs the community about the research, (2) allows investigators to learn about the community's concerns; and (3) enables community members to express their concerns to the IRB. However, the community's approval of a study is not a substitute for informed consent from the participants. The FDA's guidance also suggests that community members can refuse to participate in the study by wearing some kind of marker (such as jewelry) that indicates that they do not want to be in the study. The IRB must approve community consultation plans (Food and Drug Administration 2013).

While the guidance helps to clarify some of the issues concerning community consultation, it leaves many questions unanswered. The guidance does not describe formats for consulting the community, nor does it state how much consultation is adequate. As I have stressed many times in this book (see Chap. 4), publicity and community engagement are important for promoting public's and community's trust in research. However, investigators may regard publicity and community consultation as simply hurdles to overcome to get their research approved and they may therefore attempt to get by with minimum amount needed to satisfy the IRB (Karlawish 2008).

As one can see from the preceding discussion, research without informed consent is ethically controversial. The principle of trust offers some useful insights that can help resolve some of the ethical issues. Research on medical records may undermine trust in clinical research institutions, such as hospitals or academic medical centers, because patients may be concerned that their privacy and confidentiality will be compromised when investigators access their medical records. To promote trust among patients and community members, institutions that plan to conduct this research should inform patients upon admission that their medical records may be reviewed for research purposes and allow them to opt-out of this research (see discussion of opt-out consent below). If a patient opts out, his or her decision should be noted prominently in the medical record so that investigators will not review records without permission. Patients who opt out could sign a short form that documents their decision. This approach to medical records research would respect patients' autonomy without requiring investigators to go through the onerous task of contacting patients after they have left the institution to obtain permission to review their records. A potential drawback with this approach is that some patients may not consent to using their medical records in research, but enough probably will that the

data will still be useful. For medical records which are already in the system, the IRB could waive consent to allow researchers to have access to them.

QA/QI research could undermine patients' and the community's trust in clinical research institutions, because patients and community members might be concerned that they could be participating in risky research without consent. However, one might argue that this research might also enhance trust because patients and communities could to learn that the institution is taking measures to improve the quality of care (Faden et al. 2013). Allowing patients to opt-out of QA/QI research upon admission to a clinical research institution is not a realistic option, because QA/QI research involves entire groups of patients, such as all patients in intensive care units or emergency rooms. One cannot conduct a study in an ICU if all patients must provide consent. To help promote trust, institutions that plan to conduct QA/QI research should inform patients upon admission that such studies may take place. They should also inform patients that the research has the potential to improve the quality of their care and patient care in general, and give patients that opportunity to ask questions about the research (Faden et al. 2013). To promote the community's trust, institutions that conduct QA/QI research should issue press releases describing the results of projects that are likely to improve the quality of care.

Research on leftover biological samples may also undermine trust in clinical research, since patients may be concerned that unauthorized people will have access to their biological samples and that they may use them for purposes that they do not endorse. To promote trust among patients and community members, institutions that plan to provide researchers with de-identified leftover biological samples should inform patients upon admission that their biological samples may be used for research purposes and allow them to opt-out of this research. If a patient opts out, his or her decision should be documented and linked to his or her biological samples so that researchers will not use them without permission.[8] This approach to research on leftover biological samples would respect patients' autonomy without requiring investigators to go through the onerous task of contacting patients after they have left the institution to obtain permission to use their samples. A potential drawback with this approach is that some patients may opt-out, but probably most will allow their samples to be used. For biological samples that have already been collected, the IRB could waive consent to allow researchers to have access to this material.

Emergency medical research may also undermine trust because people in the community may be concerned that they will be subjected to risky experiments if they need emergency medical treatment. People who are fearful of participating in such research may even avoid seeking emergency medical treatment, which could threaten their life or health. Since almost anyone in the community might participate in an emergency research study if they qualify for enrollment, investigators and institutions who plan to conduct emergency medical research should make concerted efforts to reach out to people living in the area where the research will take place. Investigators should use a variety of methods for consulting the community,

[8] The revisions to the Common Rule include a simplified consent procedure for research involving biological samples or data, which will be discussed in Chap. 11.

such as: surveys of community members, focus groups, public meetings, and educational forums. Investigators should engage key stakeholders in the community, such as: political and religious leaders, public health officials, hospital administrators, and medical professionals (Diallo et al. 2005). Investigators should publicize the research in newspapers and magazines and on radio, television, websites, and social media (e.g. Facebook and Twitter). Investigators should report the results of community outreach activities to the IRB, such as information they have obtained about the community's needs and concerns, which could be useful in improving the study's research design or methods.

A key question related to community consultation is "what should be done if the community strongly objects to the proposed research?" FDA guidance does not address this issue, although it states that community consultation is not the same as community consent. Since the FDA claims that consultation is different from consent, the agency would seem to anticipate the possibility that research might take place despite strong objections from community members. However, the principle of trust recommends that IRBs should not approve emergency medical research when most community members strongly object to it, since conducting research without addressing the community's concerns could significantly undermine its trust.

Addressing objections from community members is not the same as obtaining the community's permission or consent. The concept of community consent may not be applicable to large populations, such as cities or metropolitan areas, because decisions made by community leaders may not reflect the will of the people. To obtain the consent of the community, one would need to ask members of the community to vote on the acceptability of a research project, which might not be practical. The concept of community consent makes the most sense when the community is a small, cohesive population, such as a tribe, since decisions made by community members tend to aligned with the will of the people.[9] Even when community consent takes place, it should not be viewed as a substitute for individual, informed consent (Juengst 1998b). Individuals should still have the right to refuse to participate in research approved by community leaders.

Another strategy investigators and institutions can use to promote the community's trust in emergency medical research and to respect autonomy is to provide community members with many different ways of opting-out of the study. The FDA guidance recommends that potential subjects could opt-out by wearing some sort of marker indicating that they do not want to participate in the study. People should also be able to opt-out by contacting the investigators and asking not to be in the study. Investigators give people a chance to opt-out during public meetings or other community engagement activities. They could also set up a website to allow people to opt-out online, and inform people about opting-out procedures during publicity efforts. Investigators should keep records of individuals who have asked not to participate in the protocol to avoid enrolling people in the study against their will.

[9] See Juengst (1998a, b) for a discussion of conceptual and practical problems with community consent.

5.7 Opt-Out Consent

Opt-out consent procedures, like those described above, raise ethical issues because one might question whether they sufficiently respect the subject's autonomy (MacKay 2015). Proponents of opt-out consent procedures argue that they respect autonomy and promote scientific research, since opt-in procedures (i.e. procedures in which subjects are enrolled only if they sign a form stating that they want to be in a study) result in lower enrollments and biased samples (Gulcher and Stefánsson 2000; Junghans et al. 2005). As mentioned in Chap. 2, Iceland implemented an opt-out consent procedure for its research database encompassing medical records and genealogical and genetic data (Weir and Olick 2004). All citizens were included in the database unless they opted out of the research. It is worth noting that the Icelandic government consulted extensively with members of the population before its parliament passed the law that governed this research. Community engagement included several town hall meetings. Over 700 newspaper articles and 100 television and radio programs covered the research. Polls showed that 75% of the population approved of the research before the parliamentary vote, and that 2 years after the law was passed 90% of Icelanders who had an opinion about the research approved it (Gulcher and Stefánsson 2000). Despite widespread approval of the project, some people objected strongly to it, including members of medical organizations (Annas 2000).

One might argue that opt-out consent does not provide adequate respect for autonomy because individuals (or their legal representatives) may not be aware of opportunities to opt out. Silence (i.e. not opting out) should not be equated with consent (MacKay 2015). For example, suppose that a hospital uses an opt-out procedure for research involving leftover biological samples. During the admission process, patients at the hospital are presented with many forms to review and sign, such as forms dealing with billing, confidentiality protections, consent for various medical procedures, etc. Buried somewhere in the stack of paper that patients receive is a short document informing them that they may opt out of research involving their biological samples. One might argue that this consent process would not sufficiently respect autonomy because patients may not notice the opt-out form or they may look over it quickly while reading and signing other documents. Thus, the fact that someone has not opted out of a study may not indicate that they wish to enroll in a study; it may only mean that have not paid enough attention to the study or the opt-out procedures. While opt-out studies raise the issue of whether the subject has actually consented to research participation, opt-in studies leave little room for doubt, because opting-in requires a subject take the time to read and sign a consent form.

Viewing the opt-in vs. opt-out issue from the perspective of trust, one could argue that opt-out procedures are more likely to cause distrust than opt-in procedures. Subjects are more likely to remember that they are enrolled in a study if they have expended time and effort opting in to it than if they have been merely informed that they can opt out. Also, subjects who opt in usually receive a signed consent

form for their records, whereas subjects who opt out may receive nothing. Subjects who discover that they are enrolled in research and claim that they were not aware of how to opt out may feel that they have been deceived or manipulated, which could lead them to distrust the investigators or the institution.

Because opt-out consent procedures are less than ideal, they should be used in research only when opt-in procedures are impractical. Investigators seeking approval for an opt-out procedure should provide the IRB with information related to the scientific rationale for using the procedure and the steps they will take to ensure that autonomy is respected. If investigators use an opt-out consent process, they should make sure that prospective subjects are aware of the study and have the opportunity to decide whether to opt out, which will help to ensure that individuals who are enrolled in the study have made a deliberate choice to participate, not just failed to opt out (MacKay 2015). Opt-out consent procedures should be used only for low-risk studies, such as observational research or research on patient records or biological samples, since opting out may not provide as much protection from risks as opting in (Vellinga et al. 2011).[10] Opt-out procedures should not be used if investigators will have access to personally identifiable private information or biological samples, since this research poses a greater threat to the subject's welfare and privacy than research involving de-identified samples or data (Annas 2000).

5.8 General Consent

The sharing of data and samples is important for promoting scientific progress, since science generally advances faster when researchers collaborate and pool their resources than when they work in isolation. Scientists therefore have an ethical obligation to share data and research materials. Government research sponsors, such as the NIH and NSF, also require funded investigators to share data and samples as broadly as possible (Shamoo and Resnik 2015). To promote collaboration and sharing in research, investigators frequently ask human subjects for permission to share their samples and data with other investigators working on yet to be determined future projects, and surveys indicate that about 80% of research subjects are willing to do this (Wendler 2006). This type of consent is known a general, broad, or blanket consent (Petrini 2010). General consent is common in research involving the procurement of samples or data for genetic or genomic biobanks (Weir and Olick 2004; Sanchini et al. 2016).

Some have argued that general consent is unethical because it does not adequately respect autonomy, since people may not understand what they are consent-

[10] An exception to this rule would be emergency medical research. I argued above that individuals should be able to opt-out of research. However, emergency medical research is a bit different than the examples we have been discussing, since in emergency medical research opting-out the choice is between opt-consent and no consent. One could argue that opt-out consent is more respectful of autonomy than no consent.

ing to. Subjects do not know who may use their data or samples, what they may use them for, and so on (Shickle 2006). Others have argued that general consent is ethical because subjects do not need to know the specifics concerning the use of their data and samples to understand that they may be used for a variety of research projects. Moreover, asking subjects for their permission each time an investigator requests samples or data (i.e. specific consent) would be inconvenient for subjects and investigators. Most people would not want to be contacted dozens of times for permission to use their samples or data (Wendler 2006; Petrini 2010).

While general consent may be acceptable for many types of studies, it may not be acceptable for research projects involving populations or communities who may have specific reasons not to permit certain uses of their samples or data. The Havasupai tribe (see discussion in Chap. 2), for example, objected to using their blood samples for research on mental illness, incest, and the tribe's origins. They also did not want to allow their samples to be shared with other investigators. Other research subjects may object to allowing their samples or data to be used for commercial purposes. Investigators who are studying communities or populations should try to determine whether they are likely to have specific concerns about the use of their data or samples. Community engagement may not be necessary for every type of study, but it would be appropriate if the investigators have reasons to believe that the community or population may have concerns regarding the use of data or samples. For example, the investigators studying the Havasupai tribe could have approached tribal representatives to learn about any concerns they might have had about the use of their data or samples.

To accommodate the needs unique to certain individuals or populations, investigators should give research subjects a menu of options for use of their data or samples. Options could include general consent, consent for research only on specific types of diseases, consent only for non-commercial research, or consent only for uses related to the research project they are participating in (McGuire and Beskow 2010; Master and Resnik 2013). A potential drawback of offering subjects a menu of options is that it may be difficult for investigators to keep track of what subjects have consented to, which may cause them to unintentionally violate the consent agreement. However, this problem can be overcome through good record-keeping practices (Master and Resnik 2013). Another potential problem with the menu approach is that it may be confusing for research subjects, but this problem can be overcome by developing simplified consent forms that offer clear choices to subjects (McGuire and Beskow 2010).

One of the advantages of offering subjects a menu of options for the use of their data and samples is that this can help promote trust. The Havasupai case illustrates vividly the distrust that can occur when investigators do not honor the wishes of research subjects or communities concerning the use of data or samples. The menu approach may also promote trust by assuring research subjects that the investigators are aware of their particular concerns regarding the use of their samples or data, and that they are taking steps to address these concerns.

5.9 Deception in Research

The Milgram case (see discussion in Chap. 2) illustrates some of the ethical issues that may arise when investigators deceive subjects in research. Deception can compromise informed consent and respect for autonomy, since investigators may need to withhold some types of information concerning a study to conduct the experiment (Wendler and Miller 2008a). For example, Milgram did not inform the subjects who were instructed to administer punishments that they were not really giving electric shocks to their "victims". Milgram argued that if he had disclosed this information, this would have undermined validity of the study, since the experiment would not be a genuine test of punishers' willingness to obey an authority figure (Milgram1974).[11]

One way of enhancing the consent process in experiments involving deception is to inform subjects that the research may involve deception without telling them the precise nature of the deception. Wendler and Miller (2008a) refer to this procedure as authorized deception. For example, double-blinded, placebo-controlled clinical trials are designed to prevent research subjects or investigators from discovering who is receiving the experimental treatment and who is receiving a placebo. The purpose of double-blinding is to control for the placebo effect (Wendler and Miller 2008a). The placebo effect is a well-documented phenomenon in which a patient's belief that he or she is receiving an effective treatment influences his or her response to therapy (Finniss et al. 2010). For double-blinding to be effective, there should be no noticeable differences between the placebo and the experimental treatment. For example, pills administered to patients should be the same size, shape, and color. In some cases, the placebo may even mimic some of adverse effects of the experimental treatment that subjects and investigators may be aware of, such as nausea. Blinding is a form of deception that the subjects consent to.

One potential objection to authorized deception is that it still is a form of deception and therefore compromises the consent process and respect for autonomy. One might argue that for consent to be valid, subjects should know what they are consenting to. Any form of deception prevents subjects from making a fully informed choice (Wendler and Miller 2008a). While this objection has some merit, it does not undermine the legitimacy of authorized deception. First, most us would agree that authorized deception is not inherently immoral, since many human activities that

[11] It is worth noting that investigators recently conducted a modified version of the Milgram experiment in which subjects could give each other mild electric shocks or a financial penalty. The subjects took turns being the punisher and the victim. The shocks and financial penalties were real and there was no deception. The subjects and experimenters were all female to control for gender effects. The investigators evaluated the subjects' willingness to obey authority by varying the conditions of the experiment. In one variation, the experimenter did not instruct the punisher to administer a punishment: the punisher was free to choose whether to punish. In another variation, the experimenters instructed the punishers to administer a punishment: the punisher was coerced. The punishers were more willing to administer a punishment when they were instructed to do so and they felt less moral responsibility for their actions. None of the subjects withdrew from the experiment or reported distress (Caspar et al. 2016).

we regard as ethical involve some form of deception that we agree to. For example, when you purchase a ticket to a magic show you understand that the magician will attempt to deceive you. Players in a poker game also understand that their opponents may be bluffing. Second, consent for research participation is often not fully informed because there is too much information one needs to know to be fully informed (Wendler and Miller 2008a). For example, a patient in a drug study may not know information related to the chemical's toxicology, pharmacology, or biochemistry, or all of its potential adverse effects. Most of us would agree that the patient does not need to know all of this information concerning the drug as long as he or she has enough information to decide whether to participate in the study (Wendler and Miller 2008a). One might argue that authorized deception can be ethical as long research subjects receive the information they need to know to make a sound decision concerning participation in a research study. IRBs should review research protocols and consent documents in studies involving authorized deception to ensure that prospective subjects will receive the information they need to make a sound decision (Wendler and Miller 2008a).

A potential problem with authorized deception is that it may compromise the validity of the research. For example, if Milgram had told his subjects that the experiment involved some type of deception, many of them would have guessed that the electric shocks were not real, because they would suspect that investigators would not ask them to cause significant harm to other people. Finn and Jakobsson (2007) argue that authorized deception may undermine the validity of experiments that mimic phishing emails that attempt to induce recipients to disclose private information, such as passwords or bank account numbers. If potential recipients know in advance that they may receive a phishing attack, they may be less likely to respond to it than they would have been otherwise. Investigators who are planning to use authorized deception must determine whether informing subjects about the possibility of deception will compromise the validity of the research. If authorized deception is likely to be adversely impact the scientific design of the study, investigators may ask the IRB whether it is acceptable to conduct an experiment without authorized deception.

As noted in Chap. 2, the federal research regulation allow the IRB to waive informed consent requirements for certain types of minimal risk research that could not be conducted without a waiver (45 CFR 46.116d). Thus, research involving deception, whether it is authorized or not, requires a waiver under the current regulations. The revisions to the Common Rule permit some types of psychological experiments deemed to be benign interventions to be classified as exempt research, which means they would not need to undergo IRB review. A benign intervention is brief, harmless, painless, and is not likely to have any lasting adverse impacts on human subjects. A benign intervention may not involve deception unless the subject consents to it (Department of Homeland Security et al. 2017). In either of case, risk is a key ethical and regulatory issue for conducting research involving deception, since an IRB cannot grant a waiver for more than minimal risk research, and research cannot be treated as involving a benign intervention if it involves some risk.

The risks of deceptive research can be difficult to assess because they are likely to be psychological in nature (Wendler and Miller 2008a). As noted in Chap. 2, some of the subjects in the Milgram experiments experienced significant distress, remorse, and anxiety as result of their participation. Milgram's experiments would probably not qualify as benign interventions because they had some lasting adverse impacts on the subjects. But were the risks of these experiments more than minimal? The federal research regulations define minimal risk as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102i)." Since Milgram's experiments were not routine physical or psychological examinations, an IRB would need to compare the risks of Milgram's research to the risks of daily life. Most of us experience some degree of psychological harm in daily life. For example, we may face stress at work or in the home; we may have arguments with family members or coworkers; we may even experience the death of loved one or go through a divorce. An IRB would need to compare the risks of the Milgram study to the types of psychological risks we ordinarily encounter in daily life.

Thinking about deception from the perspective of trust, deception can be highly detrimental to human relationships. If we discover that a family member, friend, colleague, or merchant has lied to us, we may no longer trust that person. Deception can be one of the most significant forms of betrayal. Since deception in research may undermine trust in investigators and institutions, it is important for researchers and IRBs to take appropriate measures to minimize the damage caused by deception. Authorized deception may help to promote trust by informing subjects that they may be deceived. If subjects understand that the research may involve deception, they may experience less of a sense of betrayal when the study is over and they learn about the nature of the deception. However, if deception goes beyond what subjects expected or involves matters that they would not want to be deceived about then authorized deception may not have salutary effects. Debriefing after the experiment is over can also help promote trust (Wendler and Miller 2008a). Debriefing should provide subjects with information about the nature of the deception and why researchers regarded it as necessary for conducting the experiment. Subjects should also have the opportunity to ask other questions about the research.

5.10 Assent

The federal research regulations require that children provide assent for research if they are capable of doing so (45 CFR 46.408). Assent is legally and ethically different from consent. A person who assents to research agrees to participate in a study; a person who provides consent authorizes participation in a study. While assent is part of consent, consent involves more than mere agreement: to consent to participate in research one must make an autonomous decision concerning participation (Faden et al. 1986; Berg et al. 2001). Thus, individuals who are not autonomous

(e.g. children or mentally disabled or ill adults who lack adequate decision-making capacity) may assent to research participation but they cannot provide consent. The federal research regulations include requirements for both the child's assent and the parent or guardian's permission in pediatric research (45 CFR 46.408). IRBs determine whether children are capable of providing assent by considering their age, emotional maturity, cognitive abilities, and other factors. Seven years old is the generally accepted age for providing assent (Wendler 2008). Children older than 14 may be able to provide legally valid consent if a court rules that they are mature or emancipated minors.

While respect for autonomy justifies obtaining informed consent, the principle would seem to not justify obtaining assent, since those who provide assent are not autonomous. However, one might argue that respect for autonomy still plays a key role in justifying assent, since autonomy does not happen all at once but develops as a person matures emotionally and cognitively. Asking a child to provide assents helps to recognize his or her maturing decision-making abilities and may also help to teach the child how to make autonomous decision (Wendler 2008).

Another reason for obtaining assent is to protect the research subject from harm (Wendler 2008). A child who participates in research against his or her will may suffer considerable stress or trauma. The child may resist the research procedures (such as blood draws) and harm himself or herself. Most commentators therefore recommend that children who refuse to assent not be enrolled in research, unless it is likely to benefit them medically (Wendler 2008). The federal research regulations state that the child's assent is not necessary if the research intervention is likely to benefit him or her medically and is not available outside of the study (45 CFR 46.408). For example, an 8-year-old child with cancer who does not want to participate in a clinical trial could be enrolled against his or her will if the trial offers him or her beneficial treatment that is not available outside of the trial.

Viewing assent from the perspective of trust, obtaining assent can play an important role in building trust between non-autonomous research subjects, investigators, and institutions. Assent, like consent, should be viewed as a process, not merely as a form to be signed. Investigators should view assent as an opportunity to establish relationships with subjects and foster trust. Investigators should be wary of enrolling subjects in research who refuse to provide their assent, because this could significantly damage trust.

5.11 Payment for Research Participation

Research subjects often receive financial compensation for their participation. The quantity of money subjects receive varies considerably, depending on the nature of the research, the amount time involved in performing research activities, and the degree of pain or risk associated with research procedures (Grady 2005). While subjects may receive $25 or less for completing a survey or providing a blood sample, healthy volunteers in Phase I drug safety studies may receive several thousand

dollars (Grady et al. 2005). Some subjects regard themselves as "professional guinea pigs" because compensation for research participation is their primary form of income (Lemmens and Elliott 1999; Elliott and Abadie 2008; Abadie 2010).

There are several reasons why investigators pay research subjects. First, payment can enhance recruitment (Grady 2005). Studies show that money is an important motivating factor for many research subjects, especially for healthy volunteers, who do not expect to receive any medical benefits from participation (Tishler and Batholomae 2002; Singer and Couper 2008; Stunkel and Grady 2011). Second, payment can reimburse subjects for their time, inconvenience, and travel expenses. Third, payment can serve as a token of appreciation for participation in research (Grady 2005).

Paying research subjects raises several ethical concerns (Grady 2005; Resnik 2015b). The first is that financial incentives for participation may interfere with a prospective subject's ability to make a free and informed choice concerning participation. The lure of money might entice a person, especially someone who is socioeconomically disadvantaged, to enroll in a study against his or her better judgment (Macklin 1981; McNeill 1997). Although the federal research regulations do not address the issue of paying human subjects for their participation, they do require investigators to minimize the potential for coercion or undue influence (mentioned above). Food and Drug Administration (2014) guidance documents and Council for the Organizations of Medical Sciences (2002, 2016) guidelines express the concern that financial incentives could constitute undue influence (or inducement).

While financial compensation may constitute undue inducement, it is not coercion because it does not involve the use of force, intimidation, or threats. Receiving money is a benefit, not harm. Although ethicists and IRB members sometimes refer to financial incentives as potentially coercive (Largent et al. 2012), this way of framing the issue confuses coercion and undue inducement (Grady 2005; Wertheimer and Miller 2008).

Second, the fact that money affects a decision does not mean that it is undue inducement, since this would imply that all paid labor involves undue inducement, which is absurd. If my neighbor's 15-year-old son agrees to mow my lawn for $20, it is likely that the offer of money has influenced his decision, because he probably would not mow it for free. However, we would not say that offering to pay my neighbor's son $20 to mow my lawn would be an undue inducement (Resnik 2015a, b, c, d). For an inducement to be undue it must have an inappropriate impact on decision-making. So, our question should boil down to: can financial incentives ever inappropriately influence the decision to participate in research?

Some have argued that financial incentives for participation can inappropriately influence decision-making by disrupting a person's judgments concerning risks and benefits. Individuals who are strongly influenced by financial motivations may disregard the risks of research so they can earn money (Macklin 1981; McNeill 1997), and some may lie about their medical conditions in order to qualify for studies or maintain enrollment (Abadie 2010; Resnik and McCann 2015).

Emanuel (2004, 2005) dismisses this concern on the grounds it does not matter whether financial incentives impact the subject's judgments concerning risks and benefits because an IRB has already approved the research and determined that the risks are reasonable in relation to the benefits. Moreover, federal guidance discourages IRBs from treating money as a benefit that could offset the risks of research (Grady 2005; Food and Drug Administration 2015). Therefore, financial incentives cannot unethically induce human subjects enroll in studies that place that involve unreasonable risks.

While Emanuel makes an important point, his reasoning is flawed. First, an IRB might approve a study without adequately reviewing the risks, which could expose subjects to unreasonable risks. Second, the subject's judgment of what makes a risk reasonable might differ from the IRB's. The subject's judgment of what makes a study too risky is a function of his or her values and beliefs. An offer of money might lead someone to take risks that are unreasonable for him or her, even if the IRB has judged that these risks are reasonable. Thus, financial incentives may undermine the subject's autonomous decision-making even if they do not lead him or her to take risks that an IRB has judged to be unreasonable (Grady 2005; Resnik 2015a, b, c, d).

If we assume that undue inducement is a legitimate ethical concern, we need to ask whether financial incentives are likely to impact risk/benefit judgments. This is an empirical issue concerning the impact of money on human cognition. Empirical studies have shown that financial incentives can increase willingness to participate in research but usually have little impact on risk/benefit judgments (Halpern et al. 2004; Singer and Couper 2008; Mantzari et al. 2014). One study found that financial incentives do not cause most subjects to discount risks but have the opposite effect: participants in this study judged higher-paying studies to be riskier than lower-paying ones and spent more time learning about studies they viewed a high-risk than those they perceived as low-risk (Cryder et al. 2010). Another study found that patients formed judgements of risk independent of the amount of money offered and were unwilling to participate in studies they perceived as too risky, even for more money (Dunn et al. 2009).

While it is important for investigators to continue to explore the impact that financial incentives have on prospective research subjects' decision-making, the evidence obtained so far suggests that money does not adversely impact most subjects' risk/benefit judgments. However, it is possible that for some subjects, such as socioeconomically disadvantaged individuals, financial incentives do impact risk/benefit judgments. For this reason, it is important for investigators and IRBs to be mindful of the possibility that excessive financial incentives may unduly induce individuals to participate in research (Resnik 2015a, b, c, d).

Though undue inducement may be a concern with offering subjects too much money, exploitation may an issue with offering them too little (Shamoo and Resnik 2006). Exploitation involves taking unfair advantage of a person or group of people in a transaction or relationship (Wertheimer 1999). From a Kantian perspective, exploitation is unethical because it disrespects human dignity and autonomy (Sample 2003). Exploitation includes three conditions: (a) the exploiter harms the

exploitee in the transaction or relationship; (b) the exploitee does not consent to the transaction or relationship; and (c) the exploiter obtains more than their fair share of the benefits of the transaction or relationship. For exploitation to occur, at least one of these three conditions must be present. Slavery, for example, involves all three conditions (Wertheimer 2011). Exploitation can happen even when both parties consent and neither is harmed if the exploiter derives an unfair share of benefits from the transaction or relationship (Wertheimer 1999). For example, suppose that John is destitute and decides to put his guitar up for collateral to obtain a loan from a pawnshop. The guitar has a market value of $500 but the pawnbroker assesses its value at $50 and loans him that amount of money. We could say that the pawn broker has exploited John because he derives more than his fair share of benefits from this transaction. For this deal to be fair, the pawnbroker would need to offer John a loan closer to the free market value of the guitar. Although exploitation is prima facie wrong, we might still decide to permit some forms of exploitation because they offer important benefits to society or because banning them would interfere with human rights. Although exploitation is wrongful, it is not always wrong, all things considered (Wertheimer 1999). For example, one might agree that pawn brokers often exploit people who receive loans from them, but decide that this business should not be banned because it offers important benefits to society and people have a right to put items up for collateral at less than their market value.

Exploitation could occur in research with human subjects if investigators, institutions, or sponsors do not share the benefits of research with participants fairly (Resnik 2003a, b, c). Human research studies often yield significant benefits for investigators (e.g. salary and career advancement), institutions (e.g. research funding), and sponsors (e.g. development of commercial products). In clinical research, subjects may receive a fair share of benefits by gaining access to medical treatment. In research on healthy volunteers who will not receive medical treatment, subjects can receive a fair share of the benefits of research by earning money for their participation. Although federal guidance discourages IRBs from treating money as a benefit, most people consider money to be beneficial. Failing to offer healthy research subjects enough money could therefore constitute exploitation (Shamoo and Resnik 2006). As noted earlier, some subjects may participate in Phase I drug trials on healthy volunteers because they need the money (Abadie 2010). Underpaying healthy volunteers in Phase I drug trials would be analogous to underpaying socioeconomically disadvantaged workers who perform risky manual labor (Shamoo and Resnik 2006; Elliott and Abadie 2008). Thus, when it comes to paying research subjects, investigators must avoid undue inducement (i.e. overpayment) and exploitation (i.e. underpayment) (Resnik 2015b).

Exploitation could occur when investigators compensate children for participating in research, since parents may enroll children in studies to obtain money for themselves. Payments to children vary considerably, depending on the nature of the research, the procedures, the amount of time or inconvenience involved, and so on. One study found that children may receive from $1 to $1000 for their participation. Payments may take to form of cash, savings bonds, or gift cards (Weise et al. 2002). An additional concern with payments in pediatric research is that parents may

coerce their children into participating in studies (Grady 2005). Some amount of financial compensation is necessary in pediatric research to encourage parents to enroll their children in studies, but compensation levels should not be excessive (Grady 2005). Some commentators have argued that payments to children should reimburse parents for their travel and time and provide children a token amount of compensation to recognize their contribution, but that payments should not be so large that they encourage parents to exploit their children for money (Committee on Drugs, American Academy of Pediatrics 1995).

A final issue related to financial incentives is that payments to research subjects may result in disproportionate (or biased) enrollment of socioeconomically disadvantaged individuals, which could undermine the generalizability of the results (Resnik 2015b). Generalizability is important for enhancing the scientific and social value of research. Unless investigators are focusing on important issues pertaining to a specific population (e.g. heart disease in women or lung cancer in African Americans), they should use research methods that promote the generalizability of their results. Disproportionate enrollment of socioeconomically disadvantaged individuals could affect generalizability if socioeconomically disadvantaged individuals have traits which are different from the general population. While most studies seek to achieve proportional representation of subjects with different demographic characteristics (e.g. gender, race, or ethnicity) most do not take socioeconomic status into account. There has been very little research on the relationship between payment and disproportional enrollment. However, one study found that payment does not increase the proportion of socially deprived or elderly people enrolled in clinical trials (Jennings et al. 2015).

Disproportional enrollment may raise issues of fairness (or justice) if the composition of the study population results in an inequitable distribution of the risks and benefits of research (National Commission 1979). For example, one might argue that it would be unfair to include mostly socioeconomically disadvantaged individuals in a study that is likely to benefit only people who are well-off (Elliott and Abadie 2008).

There are no easy solutions to the problem of disproportionate enrollment of socioeconomically disadvantaged individuals in research. One way of dealing with this problem would be offer a level of compensation proportional to the subjects' level of income so that people with higher incomes would earn more for their research participation. While this strategy might encourage more people with higher incomes to enroll in research, it would be blatantly unfair, because subjects would not receive equal pay for equal work (Resnik 2015b). Another strategy would be to actively recruit subjects from higher income groups, but this strategy might not be very effective if members of those groups are not offered enough money to make their participation worthwhile.

It is worth mentioning that the problem of disproportionate enrollment of socioeconomically disadvantaged individuals is not likely to be a problem in studies that offer subjects medical benefits, such as Phase II, III, and IV clinical trials, since patients with higher incomes are likely to be interested in enrolling studies that may benefit their health. Most diseases do not discriminate on the basis of income or

wealth: rich and poor people develop cancer, heart disease, diabetes, Alzheimer's disease, and so on. The problem of disproportionate enrollment is likely to be most acute in Phase I trials and other types of research that do not provide subjects with direct medical benefits (Elliott and Abadie 2008).

Thinking about financial incentives from the perspective of trust, underpayment is likely to have more of negative impact on trust than overpayment, because subjects who are not paid enough money may feel that they are being exploited, underappreciated, or otherwise mistreated. Ensuring that subjects are adequately compensated is a way of recognizing the value of their contributions to research. Subjects contribute their time and labor to research and often take significant risks or endure pain or other hardships in to help investigators achieve their goals. While it is important for investigators and IRBs to be mindful of how financial incentives may impact informed consent and recruitment, they should not allow these concerns to overshadow their obligation to ensure that subjects receive fair compensation for their efforts. To promote trust, consent documents should clearly describe compensation plans, e.g. how much money subjects will receive for completing different study activities, and whether payment will be pro-rated if they do not complete all study activities.

One might argue that policies which restrict the amount of money that research subjects can be payed are paternalistic and overprotective (see discussion at the end of Chap. 2). Ordinarily, we do not place limits on the amount of money that one may be paid for performing a job. If a coal company is having trouble hiring enough workers and it wants to double coal miners' wages to recruit new employees, we would have no objections to this. We would not be concerned that offering coal miners more money to perform a risky job would be an undue inducement. Indeed, we would probably be more concerned if the mining company does not offer miners enough money to perform this work, since this could be exploitative. Minimum wages laws in the U.S. and other countries were enacted to ensure that workers are adequately paid and not exploited. We have no laws concerning maximum wages. In capitalistic societies, upper limits on wages are determined by the free market, not by government regulations or ethical guidelines.

If we place limits on the amount of money that competent, adult human subjects may earn in research, we are treating research participation differently from other forms of labor. Research subjects would be protected from financial incentives that could unduly induce them to enroll in studies, but coal miners would require no such protections related to their work. We normally assume that competent adults can make sound decisions concerning payment for employment. If a coal company wants to offer miners more money, we would not say that the prospective employees cannot make sounds decisions concerning working for the company. We would usually assume that prospective employees can consider the risks and hardships associated with coal mining and decide whether the amount of money offered by the company is adequate compensation for those risks and hardships.

What, if anything, justifies treating human research participation differently from other forms of employment? Why are we concerned about paying competent, adult human subjects too much money but we are not concerned about paying coal

miners too much money? There are several potential answers to these questions. The first is that participation in human research is so risky that it needs to be treated differently than other types of human labor. But this answer is factually incorrect: research participation is no more risky than other types of work (Wendler 2011). Indeed, in some ways participating in research is much safer than other forms of labor involving risks, such as coal mining, construction work, firefighting, etc.

The second is that the decision to participate in research is so difficult (i.e. fraught with so many complexities and conflicting values) that we need to protect adults from making poor choices. This answer is also mistaken because deciding whether to participate in research is not more difficult than other choices we allow competent adults to make without excessive protection, such as the decision to buy a new home, enlist in the military, marry, or donate a kidney.

The third is that paying research subjects treats the human body as a commercial product, which threatens human dignity (Radin 1996; Andrews and Nelkin 2001). If people are not paid for donating blood, they should also not be paid for providing a blood sample for research. This answer is also unsatisfactory because a great deal of human research does not involve treating the body as a commercial product in any form. For example, paying someone to answer a survey question does not involve commercializing the human body. Moreover, paying someone for providing a blood sample could be viewed as compensating them for their time or inconvenience, not for their blood.

The fourth is that we think that people should participate in research because they want to do some good for society, not because they want to earn money. Research participation should be an altruistic activity. Payments should be limited to direct reimbursement for expenses. Wertheimer (2011, p. 118) characterizes this position as the idea that "payments are a necessary evil, but an evil nonetheless." The trouble with this position is that there is no convincing ethical reason why we should think that research participation must be an altruistic activity. Subjects often participate in clinical trials for selfish reasons, such as to gain access to experimental treatments that may benefit them (Menikoff 2006). If we have no problem with patients participating in clinical trials to obtain medical benefits, why should we object to healthy volunteers participating in research to earn money? While it would be a good thing if people participated in research only for altruistic reasons, there is nothing inherently wrong with participating in research for selfish reasons, including the desire to earn money.

A fifth possible answer places our moral qualms about payment in historical context. In Chap. 2 I argued that one reason why the U.S. and other countries have adopted paternalistic and protective research regulations and guidelines is to promote public trust. The regulations and guidelines help to assure the public that rules are in place to protect the rights and welfare of human subjects and to avoid repeating the mistakes of the past. Restrictions on payments are necessary, one might argue, to assure the public that human subjects will be protected from taking excessive risks or compromising their values to earn money. The problem with this answer is that compensating research subjects for their participation is not likely to expose them to unreasonable risks or undermine their autonomy, since there are

rules in place, such as requirements concerning IRB review, risk minimization, and informed consent, which are designed to protect the rights and welfare of human subjects (Emanuel 2005; Wertheimer 2011). If these rules did not exist, then paying research subjects for their participation would indeed raise major ethical concerns. But since we have such rules, it is difficult to understand why so many people have moral qualms about paying research subjects. Perhaps the payment guidelines we have developed are an overreaction to past abuses, and our concerns about paying research subjects are misplaced (Wertheimer 2011).

Box 5.1: Payment Models

Grady (2005) describes several different approaches to paying research subjects, each of which have advantages and disadvantages. According to the market-approach, institutions should subjects pay subjects according to the free market value of their labor. The amount of money paid to subjects would be a function of supply and demand: wages would increase as demand goes up and supply goes down, or decrease as supply goes up and demand goes down. One main advantage of this approach is that it would allow institutions and sponsors to adjust compensation levels to deal with problems related to recruitment. For example, if an investigator is having trouble recruiting subjects for a Phase I drug study, the sponsor could increase the payment level. Another advantage is that it allows institutions to tailor payments to risk, pain, or inconvenience. For example, a study could offer more money for a skin biopsy than a blood draw. A final advantage is that this approach treats human research participation as similar to other forms of paid labor, which might encourage institutions and sponsors to offer the kinds of protections for human subjects which they provide to other paid employees, such as worker's compensation. However, since this approach places no upper or lower limits on payments, it has the potential for both undue inducement and exploitation (Resnik 2015b). According to the reimbursement approach, payments should only reimburse subjects for their expenses, such as travel and lost wages (Grady 2005). An advantage of this approach is that it probably would not lead to undue inducement, since subjects would not be paid more money than they are already earning. A disadvantage of this approach is that it would be unfair, since subjects with higher incomes would be paid more than those with lower incomes, due to differences in lost wages. Another disadvantage of this approach is that it would not allow investigators to increase compensation levels to boost recruitment (Resnik 2015b).

According to the token appreciation approach, institutions should pay subjects a nominal amount of money to as a sign gratitude for their help (Grady 2005). Because payment levels would be low, this approach would not lead to undue inducement, but it could lead to exploitation. Low payments levels could also hurt recruitment, especially if the research involves significant pain, discomfort, or risk.

(continued)

Box: 5.1 (continued)

According to the wage-labor model, subjects should be paid a standard wage for their time roughly equivalent to what someone would earn for unskilled labor (Grady 2005). For example, since a typical unskilled laborer in the U.S. earns between $8 and $12 per hour, the rate for research participation could be set at $10 per hour (Grady 2005). This approach would probably would not lead to undue inducement or exploitation, since compensation levels would not be very high or unfairly low (i.e. they would be a little above minimum wage). However, this approach would not allow investigators to increase compensation levels to address problems with recruitment, nor would it allow investigators to adjust payments according to the amount of pain, discomfort or risk involved in research.

It may the case the best way compensating research subjects is to use some combination of these different approaches, depending on the situation. For example, for pediatric research the child could receive a gift card as a token of appreciation for his or her contribution and the parent could receive reimbursement for expenses. For survey research, subjects could receive a payment based on the hourly rate for unskilled labor, which could be increased if recruitment lags. For a laboratory assay development study involving the collection of different types of biological samples, subjects could be paid per type of sample provided and reimbursed for their time and travel.

5.12 The Right to Withdraw

The right to withdraw from research participation has been an ethical requirement since it was incorporated into the Nuremberg Code (1949). Federal research regulations require that investigators inform subjects that they "may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled (45 CFR 46.116a8)." The right to withdraw is also part of the Helsinki Declaration (2013) the Council for the International Organizations of Medical Sciences guidelines (2002, 2016). Informed consent documents typically inform subjects that they can withdraw at any time for any reason without penalty and that they may refuse to participate in any research activity (Edwards 2005; Schaefer and Wertheimer 2010). Consent documents also usually inform subjects about requesting to have their biological samples destroyed and data removed from the study if they withdraw. However, it may be difficult or impossible to fulfill this request if samples or data are anonymous or have already been shared with other investigators (Melham et al. 2014). Payments may be pro-rated to ensure that subjects who withdraw receive the money that they have earned (Grady 2005). The right to withdraw is usually interpreted as inalienable, which means that one cannot voluntarily waive or restrict this right (Edwards 2005; Chwang 2008).

Although an inalienable right to withdraw is widely regarded as an important protection for human research subjects, one might still question its ethical justification (Schaefer and Wertheimer 2010). The first argument against this right is that it is incompatible with our understanding of the relationship between autonomy and contractual responsibility (Edwards 2005; Chwang 2008). Part of what it means to be an autonomous decision-maker is to accept responsibility for one's choices and actions. We normally hold competent adults responsible for their choices related to informal agreements or formal contracts. Part of what it means to make an agreement is to limit some of your rights so you can obtain the benefits of the agreement. The other party has the right deny you certain benefits or penalize you if you do not live up to your end of the bargain. If the contract is legally valid, the courts will enforce it. For example, if you sign a contract to rent an apartment and do not pay your rent on time, the landlord may take steps to evict you. If you break the lease before it expires, you may face a financial penalty. Informed consent can be viewed as an agreement between the subject and investigator (Berg et al. 2001; Manson and O'Neill 2007). If people are allowed to limit their rights in other types of contracts, they should also be able to limit their rights in research agreements, including theirs right to withdraw. Thus, the right to withdraw should alienable (Chwang 2008).

The first argument is not a compelling reason to reject an inalienable right to withdraw, because other considerations, such as protecting human life or welfare, may sometimes take precedence over allowing people to alienate some of their rights (McConnell 2010). One might argue that states can place some limits on the ability to alienate one's right to life to preserve life and protect people from harm (Feinberg 1978). For example, dueling, Russian roulette, euthanasia, and assisted suicide are illegal in many states. As John Stuart Mill famously argued, one should not be allowed to alienate one's right to liberty by selling one's self into slavery (Mill 1978). Though Mill claimed that selling one's self into slavery should not be permitted because it would undercut the very foundation of liberty, one could also argue that it should not be permitted because it would threaten one's life or health. Likewise, one might argue that we should not allow people to alienate their right to withdraw to protect them from harm (McConnell 2010).

The second argument against an inalienable right to withdraw is that sometimes withdrawing may place the research subject at risk (Resnik and Ness 2012). For example, if a subject has been taking an experimental medication in a clinical trial, and stopping the medication suddenly is likely to result in adverse withdrawal effects, then they may place their own health at risk if they stop participating in the trial. In a case like this, the right to withdraw could be restricted to protect subjects from harm. Subjects would be allowed to stop participating in a study only if they follow a medication withdrawal protocol.

The second argument is not compelling reason for rejecting an inalienable right to withdraw, since subjects could taper off their medications without participating in the study. Patients who want to withdraw would be allowed to take the experimental medication under a doctor's supervision even though they would no longer be research subjects.

A third argument is that withdrawing from research may also place other people at risk in some rare situations (Resnik and Ness 2012). For example, suppose that a subject is participating in a clinical study of a medication used to treat a dangerous communicable disease, such as tuberculosis (TB). If the subject stops taking the medication, he or she may become contagious and transmit the disease to other people, which would threaten public health. Or suppose that a subject is participating in a pig-human xenotransplantation study and there is a risk that he may contract a disease (i.e. a zoonosis) from a pig organ he receives and spread it to other people (Spillman and Sade 2007). The study includes procedures for monitoring subjects for zoonoses and controlling the spread of those diseases. If the person withdraws from the study, he may place the public health at great risk. In cases like these, the right to withdraw could be limited to protect the public's health.

The third argument is also not a compelling reason for rejecting an inalienable right to withdraw because there are ways of protecting the public's health that do not require the subjects to continue participating in research. The TB patient could receive treatment for the disease without remaining in the study, and the recipient of the pig organ could be monitored for zoonoses without continuing to participate in the xenotransplantation study.

A fourth argument is that withdrawing from research may compromise the study itself if loss of a research subject will undermine the statistical power of the study (Chwang 2008). This is a weak argument against the right to withdraw since a) the loss of one subject is not likely to significantly affect the statistical significance of the results; and b) it may be possible to enroll additional subjects to meet the target sample size.

Given there are some arguments against an inalienable right to withdraw from research, what are the arguments in favor of it? One might be tempted to say that granting subjects a right to withdraw is necessary to protect them from coercion. A person should not face a threat of harm or loss of benefit if they decide to stop participating in a study. However, this position confuses coercion with the enforcement of prior agreements (Chwang 2008). For example, if I threaten to damage your car if you do not give me ride to my home, this would be coercive. However, if I agree to pay you for gas if you give me a ride home and you demand gas money once we arrive, this would not be coercive because you are enforcing our prior agreement. One could argue that penalizing a subject for withdrawing is a way of enforcing this agreement: it is not coercion.

A better justification is that an inalienable right to withdraw is necessary to protect subjects from harm. Subjects may not be able to anticipate how they will react to different research procedures and they may change their minds about participation when they experience some undesirable effects, such as pain, discomfort, nausea, dizziness, claustrophobia, etc. (Edwards 2005; Schaefer and Wertheimer 2010). If a subject develops intolerable symptoms or becomes anxious about possible adverse effects, he or she should be able to withdraw without penalty. If a subject faces a penalty for withdrawing, he or she may place his or her own health at risk by remaining in the study or not telling the investigator about the problems he or she is experiencing.

Approaching these issues the perspective of trust, we can construct another rationale for the right to withdraw: the right is justified because it helps to promote trust between research subjects and investigators and institutions, as well as the public's trust in the research enterprise (Schaefer and Wertheimer 2010). Subjects may want to be assured that they can withdraw from a study without penalty, especially if they are experiencing adverse effects. This assurance can enhance their trust in the investigator and the institution. The right to withdraw can promote the public's trust in the research enterprise by helping investigators, institutions, and sponsors to avoid potentially disastrous situations involving harm to human subjects. For example, the public could become outraged if it learns that a subject died in an experiment because they remained in the study to avoid a financial penalty for withdrawing. To avoid this adverse negative publicity associated with type of potential tragedy, subjects should be able to withdraw at any time without penalty.

Before concluding this section, it is worth noting that by granting human subjects an inalienable right to withdraw we are providing them with more protection from harm than people normally receive outside of the research context. Outside of the research context, we allow competent adults to face financial penalties for breaking contracts. In some cases, people may place themselves at some risk of harm to avoid these penalties. For example, a person who has developed an allergy to the carpeting in his apartment might remain in the dwelling until his lease expires to avoid a financial penalty. Likewise, a professional athlete might place his health at risk in order to penalties built into his contract. Though some might regard these added safeguards for human subjects as paternalistic and overprotective (Chwang 2008), I have argued that they can justified as a means of protecting subjects from harm and promoting trust.

5.13 Conclusion

In this chapter I have applied my trust-based approach to a variety of issues related to informed consent in research, including disclosure standards, documentation, consent by parties other than the subject, research without consent, opt-out consent, general concept, deception, assent, payment for research participation, and the right to withdraw. Although the federal regulations provide considerable guidance pertaining to informed consent, ethical issues still arise due to controversies concerning the interpretation of the regulations, conflicts between ethical principles (e.g. respect for dignity/autonomy vs. beneficence) and the need to acknowledge local customs and traditions concerning consent. I have argued that trust plays a key role throughout the consent process and that reflecting on the importance of promoting trust can help us address ethical issues pertaining to consent. In the next chapter, I will examine the relationship between trust and privacyand confidentiality.

Chapter 6
Privacy and Confidentiality

In the previous chapter, I examined the ethical issues informed consent in research and argued that thinking about the importance of trust can help us address this issues. In this chapter I will continue some of the themes developed in the previous chapter by reflecting on the relationship between trust and protection of privacyand confidentiality. I will also consider how the trust-based approach deals with some ethical dilemmas related to protecting privacy and confidentiality in research.

6.1 Privacy, Confidentiality, and Trust

Privacy and confidentiality are distinct concepts. Privacy refers to freedom from unwanted intrusion into one's private affairs. Privacy includes physical privacy (i.e. freedom from unwanted invasions of one's body or private space), decisional privacy (i.e. freedom from unwanted interference in one's private decisions), and informational privacy (i.e. freedom from unwanted disclosures of private information). Private information is information linked directly to the individual for which there is a reasonable expectation of privacy. Private information includes: medical records, research records, social security numbers, bank and credit card statements, and personnel records. A social scientist who observes customers and merchants interacting at a grocery store would not be invading privacy because the store is a public area and there is no reasonable expectation of privacy. Likewise, information which is in the public domain, such as birth and death records, is not considered private. Confidentiality refers to protection of private information. Thus, confidentiality addresses one aspect of the broader notion of privacy, i.e. informational privacy (Hodge and Gostin 2008).

As argued in Chap. 4, protecting the privacyand confidentiality is important not only for respecting dignity/autonomy and preventing harm but also for promoting trust. We usually share our secrets only with individuals whom we trust, such as

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close friends, family members, or professionals, e.g. doctors, lawyers, counselors, etc. (Bok 1989). Someone who discloses a secret without permission violates the trust that has been placed in them and damages the relationship. Most professional codes of ethics include a duty of confidentiality. For example, the Hippocratic Oath states that "Whatever I see or hear in the lives of my patients, whether in connection with my professional practice or not, which ought not to be spoken of outside, I will keep secret, as considering all such things to be private (National Library of Medicine 2012)." The American Medical Association's (2001) ethics code states that a physician shall "safeguard patient confidences and privacy within the constraints of the law."

Breaches of confidentiality or privacy can seriously damage subjects' and community's trust in investigators and institutions, as well as the public's trust in the research enterprise. For example, mammography patients and members of the local community and general public were outraged in 2010 when they learned that someone had hacked into a University of North Carolina server containing the personal information of 180,000 mammography patients from around the state. The university determined that the investigator in charge of database security, radiology professor Bonnie Yankaskas, neglected her duties and should be terminated or demoted. Faculty members came to her defense, however, and argued that the university was trying to make her into a scapegoat. Yankaskas claimed that she did not have the technical expertise or training needed to keep the research database secure (Kolowich 2011). The university and Yankaskas reached a legal settlement in 2011. Under the terms of settlement, the university agreed to restore Yankaskas status as a full professor and pay her legal fees, and Yankaskas agreed to retire by the end of 2011 (University of North Carolina at Chapel Hill 2011).

In February 2008, someone stole a laptop computer containing medical information on 2500 patients enrolled in a clinical trial conducted at the National Institutes of Health (NIH). The laptop, which was stolen from an employee's locked automobile trunk, contained information pertaining to diagnoses, clinical trial data, and laboratory test results. The person who stole the computer potentially had access to private information because the data on the laptop had not encrypted, which was a violation of the NIH's computer security policy. NIH officials did not inform the patients of the security breach until nearly a month after it occurred because they did not feel that the patients were at immediate risk and they did not want to unduly alarm them (Nakishima and Weiss 2008).

As mentioned in Chap. 2, federal regulations require that research protocols include appropriate provisions for protecting privacyand confidentiality (Department of Health and Human Services 2009, 45 CFR 46.111a7). They also require that investigators inform subjects about measures that will be taken to protect their confidentiality (45 CFR 46.116a5). The revisions to the Common Rule address some privacy and confidentiality research involving biological samples or data, which will be discussed in Chap. 11 (Department of Homeland Security et al. 2017). The Helsinki Declaration (World Medical Association 2013) and Council for the Organizations of Medical Sciences (2002, 2016) guidelines also include statements concerning the obligation to protect privacy and confidentiality.

The privacy rule of the Health Insurance Portability and Accountability Act (HIPAA) includes requirements pertaining to protecting the confidentiality of private health information (PHI) contained in medical records (National Institutes of Health 2004). Hospitals, clinics, and other entities covered by HIPAA are required not to disclose PHI without the patient's permission. Researchers who are working for or with covered entities may obtain PHI if patients sign a consent document granting them access it. As noted in Chap. 5, a privacy board or an IRB can allow investigators to have access to PHI without the patient's consent for certain types of research, such as research involving medical records or preparations prior to research, such as determining how many patients might be eligible for a clinical trial. Additionally, covered entities may disclose PHI without consent for public health and criminal law purposes, including reporting of abuse or neglect, infectious diseases, and stabbings or gunshot wounds (Gostin 2001). A health care professional who violates patient confidentiality while conducting research may also be liable under federal law and state medical malpractice or confidentiality laws (Hodge and Gostin 2008).

Some measures for protecting privacyand confidentiality in human subjects research include: (1) limiting access to data or biological samples to members of the research team; (2) storing data securely; (3) using passwords, encryption, firewalls, and other computer security practices to protect electronic records; (4) training research staff on confidentiality and privacy procedures; (5) removing personal identifiers from data or samples and marking them with a code; (6) obtaining a Certificate of Confidentiality (CoC) from the Department of Health and Human Services, which allows investigators to resist court orders for access to data (Hodge and Gostin 2008).[1]

Informed consent documents and discussions should provide research subjects (or their representatives) with information about measures investigators will use to protect confidentiality, as well as circumstances in which they may be required by law to breach it (discussed below). A useful phrase to include in a consent document would be "We will protect your confidentiality to the maximum extent allowed by law" or something to that effect. Informing research subjects of measures used to protect confidentiality helps to promote their trust (Hodge and Gostin 2008).

Investigators should inform the IRB as soon as possible of a breach of security or confidentiality, so that the committee can provide guidance on how to deal with it. Although breaches of confidentiality or security can be embarrassing for investigators and institutions, it is far better to inform subjects in a timely fashion about these problems when they arise, instead of allowing them to fester. Subjects may be understandably upset if investigators do not inform them of breaches in a timely fashion, or if they learn about breaches from a third party (such as the media).

[1] The extent of confidentiality protections provided by CoCs is not well-established, since very few cases have tested the limits of CoCs. In one case, a court allowed a criminal defendant to gain access to confidential research records protected by a CoC to obtain evidence that could be used to discredit the testimony of a witness for the prosecution. The defendant's attorney wanted to know whether the witness was in a research study protected by a CoC (Beskow et al. 2008).

Communications with subjects should describe the breach, what is being done to prevent it from happening again, and whether subjects are at increased risk. Such communications, if conveyed respectfully and contritely, can promote trust.

Although the duty to protect privacy and confidentiality has a strong basis in ethics and the law, it may sometimes conflict with other legal or ethical duties, such as the obligation to share data or research materials or the obligation to protect individuals or the public from harm. This chapter will examine some of the dilemmas that can arise when the duty to protect privacy/confidentiality conflicts with other obligations.

6.2 Sharing and Publishing Data and Samples

Openness—the sharing of data, materials, methods, and results—is essential for scientific collaboration and progress (Shamoo and Resnik 2015). U.S. government agencies, including the NIH and NSF, require funded investigators to share data and materials with other researchers and publish their data and results.[2] Most scientific journals require investigators to make supporting data, methods, and materials available to other researchers as a condition of publication.[3] Professional codes of ethics also endorse open sharing of data and materials and publication of data and results (Shamoo and Resnik 2015). Sharing and publication may conflict with protecting privacy and confidentiality, however, since the sharing of data and samples may allow investigators outside the research team to have access to private information concerning human subjects.

Removing personal identifiers (such as name, address, phone number, or social security number) from data or samples can help investigators protect confidentiality and privacy when sharing or publish data or samples. In the past decade, however, scientists have developed statistical methods for re-identifying individuals in genomic and medical databases, which call into question the effectiveness of de-identification as a strategy for protecting privacy and confidentiality in genomic research (Lin et al. 2004; McGuire and Gibbs 2006). One method of re-identifying an individual is to sequence a sample of that person's DNA and compare it to DNA sequences in genomic database (Lin et al. 2004; Homer et al.

[2] According to the NIH: "It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public. PIs and funding recipient institutions are expected to make the results and accomplishments of their activities available to the research community and to the public at large (National Institutes of Health 2016a)." It is important to note that until recently some European countries have had laws that restricted access to private health information and inhibited broad sharing of human subjects data. In 2015, the European Union agreed upon legislation to member nations to permit broad sharing of private health information for scientific research (Medical Research Council 2017).

[3] According to the Nature Publishing Group (2017): "A condition of publication in a Nature journal is that authors are required to make materials, data, code, and associated protocols promptly available to readers without undue qualifications."

2008). Personally identified DNA sequences may be available from military, criminal, or health care databases. If one cannot get access to these databases, it may be possible to get a sample of that person's DNA from bodily fluids or tissues they have left behind on food, cups, clothing, cigarettes, or tissues. Years ago it would have been prohibitively expensive to sequence someone's DNA to identify them in a database, but cost is now less of an impediment, due to widespread availability of relatively inexpensive DNA sequencing services (Resnik 2010a). Another method of re-identifying an individual is to construct a profile of that person based on demographic, genomic, or health care information in the database (Lowrance and Collins 2007). For example, if one knows that a research subject is a 53-year, female physics professor at Harvard University it may be possible to identify that person in a faculty listing based on this information.

The upshot of recent work on re-identifying individuals is that de-identification no longer guarantees confidentiality of genomic data (McGuire and Gibbs 2006). Scientists have therefore begun pursuing other strategies for protecting confidentiality and privacy of genomic data. One of these is to use contracts for sharing data or samples with investigators and institutions. A data use agreement (DUA) is contract for sharing data which spells out conditions for using and storing the data. DUAs usually prohibit recipients from sharing data without permission or attempting to re-identify individuals in de-identified datasets. A material transfer agreement (MTA) is a contract for sharing research materials, such as cells, tissues, animals, or chemical reagents, which spells out conditions for using the materials. MTAs may also prohibit recipients from sharing samples without permission or attempting to re-identify individuals in de-identified samples (Resnik 2010a). In 2007, the NIH required funded investigators to deposit human genomic data on publicly available websites, but it revised this policy in 2009 as a result of advances on re-identification.[4] Under the new policy, the NIH requires institutions to sign DUAs to obtain access to human genomic data. Some degraded human DNA, i.e. DNA with sequences removed that could be used to identify individuals, is still available on NIH websites (Resnik 2010a).

Although DUAs and MTAs can help protect privacy and confidentiality, they have some limitations. First, DUAs can be an administrative inconvenience for investigators. It is much easier to access data on a publicly available website than to obtain data via a DUA. Second, DUAs and MTAs do not provide unqualified protection for confidentiality and privacy, since investigators or institutions might violate them. Violators would still be liable under contract law, but it is not clear that these legal implications would always deter violators, since institutions might not sue for breach of contract.

Some investigators have responded to the conflict between openness and confidentiality by asking genomic research subjects to forego traditional confidentiality and privacy protections. To participate in the Personal Genome Project (PGP), subjects must agree to make their personally identified genomic, demographic, and

[4] Putting data on a publicly available website is tantamount to publication, since this makes the data available to the public.

medical data available on a public website (Church 2005; Lunshof et al. 2008). The project was initially piloted on a group of subjects with a background in genetics or genetic counseling, who were motivated to participate by their desire to advance scientific research and probably understood the implications of waiving traditional confidentiality and privacy protections (Church 2005). The project has expanded its enrollment since then to include subjects without a background in genetics or genetic counseling. Over three thousand participants are enrolled in the study (Ball et al. 2014). One of the benefits of the project to participants is that it provides them with access to their genetic test results (Lunshof et al. 2008). Asking participants to forego traditional confidentiality protections does not necessarily violate the federal research regulations, since the regulations only require that confidentiality and privacy protections where they are appropriate (45 CFR 46.111a7). One could argue that confidentiality and privacy protections are not needed if one of the aims of the study is to make data widely available and the subjects agree to waive these protections (Lunshof et al. 2008).

Risks related to the public disclosure of private information are an important ethical concern with the PGP. Research subjects could experience discrimination, stigma, or embarrassment as result of such disclosure. Presumably, the subjects are aware of these risks when they consent and decide to accept them to help advance the goals of the study (Ball et al. 2014). However, the family members of research subjects also face these risks, since it may be possible to predict that a family member is likely to have a genetic trait or medical condition, based on their genetic relationship to the participant (Resnik 2010a). To address this issue, the PGP requires that if someone with a monozygotic (i.e. genetically identical) twin wants to enroll in the study their sibling must also agree to enroll (Church 2005). However, other closely-related family members could also face risks. For example, if one knows that someone is the mother of a participant in the PGP, and the participant has a genetic mutation associated with an 80% lifetime risk of breast cancer, then one could predict that the mother has a 50% chance of having this mutation. Someone might be able to use this information to discriminate against the mother of the participant. One might argue that PGP is unethical because it imposes significant risks on family members of the participants without their consent (Resnik 2010a). Relatives of Henrietta Lacks (see case discussion in Chap. 1) objected to the publication of the HeLa cell genome sequence without their consent, since the genome contains genetic information that can be linked to family members (Yandell 2013). (I will discuss risks to third parties in greater depth in Chap. 7.)

Protecting privacy and confidentiality is also an important concern when investigators publish non-genomic data. To protect privacy and confidentiality when publishing non-genomic data, researchers can remove personal identifiers and use pseudonyms, numbers, or general descriptors to refer to subjects. If investigators are planning to publish photographs or images of research subjects, they should remove or black out identifying features. Sometimes research subjects may permit or even encourage investigators to use their real names or to publish photos or images with identifying features. If subjects freely consent to the publication of identifying information, there is nothing wrong with this practice.

Protecting privacy and confidentiality can also be an important concern when investigators publish research on communities (Resnik and Kennedy 2010). For example, suppose that investigators who are studying sexually transmitted diseases, drug abuse, and prostitution in a medium-sized Appalachian town discover that the local population has 50% higher rates of HIV and drug abuse compared to other towns of the same size. People who live in the town may be concerned that publishing the research results will lead to discrimination, stigma, and bias against members of the community. Removing information which identifies the community (such as name or precise geographic location) from articles submitted for publication could help protect the community from harm. However, removing this information may compromise the validity or usefulness of the results. For example, suppose that investigators plan to publish their research on the impact of natural gas extraction on the health of a local community. It may be important for other investigators to know where the community is located, so they understand the interaction between natural gas extraction and factors in the local environment (such as sources of drinking water, stream flows, infrastructure, etc.). If investigators include the location of the community in their reports, other people will be able to identify the community, which could result in harm to the community. To protect communities from harm and promote their trust, investigators who are studying communities should discuss their publication plans with representatives from those communities. Publication plans should balance scientific and community interests (Resnik and Kennedy 2010). (Chap. 7 will include additional discussion of the obligation to protect communities from harm.)

6.3 Justifiable Breaches of Privacy and Confidentiality

Although investigators have ethical and legal duties to protect privacy and confidentiality, situations may arise in which they may consider breaching privacy or confidentiality to protect human subjects, third parties or the public from harm. In these situations, the breach of confidentiality may negatively impact subjects' trust in investigators. Thus, to justify a breach of confidentiality one must decide that other moral considerations (such as preventing harm) take precedence over maintaining secrecy and promoting the subject's trust.

6.4 Harm to Self

Sometimes investigators must decide what to do when they discover that research subjects intend to harm themselves (Vannoy et al. 2010; Resnik et al. 2015a, b, c, d). Suppose that during an interview a psychiatric research subject expresses a strong desire to kill himself. He also talks about how, when, and why he would commit suicide. In this case, the investigator would face a conflict between beneficence (i.e.

the duty to protect the subject's life/health) and respect for autonomy (i.e. the duty to honor the subject's right to control private information about himself) and trust (i.e. the duty to promote the subject's trust). One could argue that in this case beneficence should take precedence over autonomy and trust, because a person who expresses a strong desire to kill himself may be suffering from a mental or emotional affliction, such as depression, grief, anxiety, or psychosis, which compromises decision-making. Since the subject may not be fully autonomous, some form of paternalistic intervention may be warranted. The intervention could include calling 911,[5] offering to take the person to a local crisis center or emergency department, or contacting the person's family, depending on the situation (Smith et al. 2017). If the person conducting the interview is a staff member, she should inform her supervisor about the situation and take appropriate action while waiting for further instruction. Investigators and staff members must exercise discretion and good judgment when dealing with subjects who express suicidal thoughts, since people sometimes talk about suicide but do not intend to go through with it. Investigators and staff members should follow standard operating procedures for responding to suicidal ideation by research subjects (American Psychiatric Association 2003; Vannoy et al. 2010). If an investigator determines that a person who expresses suicidal thoughts is not a high risk for suicide, then it may not be appropriate to breach that person's confidentiality and betray their trust. A wiser course of action might be to ask the person if they would be interested in a referral for counseling or the phone number of a suicide hotline.

6.5 Harm to Others

Investigators also face moral dilemmas when they discover that research subjects intend to harm other people (Resnik et al. 2015a, b, c, d).[6] Suppose that during a phone interview a research subject says that he wants to bomb a department store franchise that he blames for damaging the local economy and costing him his job. The investigator believes that the subject is not joking and that his threat is serious. In this situation, the investigator would face a conflict between beneficence (i.e. the duty to prevent the subject from harming others) on the one hand and respect for autonomy (i.e. the duty honor the subject's right to confidentiality), non-maleficence (i.e. the duty not to harm the subject) and trust on the other. Even the most enthusiastic supporters of liberty and autonomy would admit that we can restrict a person's actions or decisions to prevent him or her from inflicting serious harm on others. If

[5] In the U.S., 911 is the phone number for emergency services, i.e. police, firefighters, ambulance, etc.

[6] The National Institute of Environmental Health Sciences conducted a study on the health risks associated with participation in cleanup activities related to the oil spill in the Gulf of Mexico in 2010. Some of the subjects in the study threatened to harm themselves of others during interviews. See Resnik et al. (2015a).

a person intends to harm someone else, we are justified in taking action to stop them from carrying out that threat, including breaching their confidentiality (Beauchamp and Childress 2012).

A famous court case addressed the issue of breaching confidentiality to prevent harm to others. In the summer of 1969, Prosenjit Poddar, a graduate student at the University of California at Berkeley, confided to his psychotherapist, Dr. Lawrence Moore, that he wanted to kill Tatiana Tarasoff when she returned from a trip, because he was angry that she did not want to have a romantic relationship with him. Dr. Moore called the campus police and recommended that Poddar be civilly committed because he was suffering from a mental illness (schizophrenia) and was dangerous to himself or others. The police detained Poddar but determined he was not dangerous and released him shortly thereafter. Moore's supervisor, Dr. Harvey Powelson, told Moore not to have Poddar detained again. Neither Moore, nor Powelson, nor the campus police told Tarasoff about Poddar's threat to kill her. On October 27, 1969, Poddar stabbed Tarasoff to death. Tarasoff's parents sued Moore and the university for negligence, arguing that they had failed to exhibit reasonable care by failing to warn Tarasoff about the threat. After lower courts ruled in favor of the plaintiffs, the defendants appealed the case to the California Supreme Court, which upheld decisions made by the lower courts. The court ruled that Dr. Moore had a duty to warn Tarasoff about Poddar's threat. The professional duty of confidentiality does not allow one to ignore threats to public health and safety (Tarasoff v. Regents of the University of California 1976).

The Tarasoff case has had a significant impact on the law concerning professional confidentiality and the duty to protect the public from harm. Numerous state courts have followed or cited the Tarasoff ruling and some state legislatures have adopted laws that require psychotherapists or other health professionals to breach patient confidentiality to protect the public from harm (Walcott et al. 2001). However, the case remains controversial. Some courts have rejected the ruling in Tarasoff, while others have limited professional obligations to protect the public from harm. For example, some courts have ruled that for there to be a duty to warn others the person must communicate a specific threat to harm a specific person (Walcott et al. 2001). Organizations representing professional psychologists and psychiatrists have objected to the Tarasoff decision on the grounds that requiring therapists to breach confidentiality to protect the public from harm would interfere with clinical practice and undermine patients' trust (Felthous 1999; Walcott et al. 2001).

A key issue relevant to breaching confidentiality to protect other people from harm is evaluating the nature of the risk. People sometimes threaten to harm others when they are angry or distraught, and it can be difficult to decide whether these threats are genuine, especially if one does not have a longstanding relationship with the person. If an investigator overreacts to an idle threat made by a research subject and warns the authorities, he or she may damage the subject's trust irreparably and cause the research subject unnecessary harm (such as the stress of being questioned or arrested by the police). Investigators should therefore carefully consider the nature of the risk that the subject poses to others before taking action. To breach confidentiality when a research subjects threatens someone else, an investigator should have

credible evidence[7] that the subject intends to seriously harm a specific victim (or victims) and that the danger is imminent (Felthous 1999; Beauchamp and Childress 2012). Investigators and staff members should follow standard operating procedures for responding to threats made by research subjects (Resnik et al. 2015a, b, c, d).

6.6 Suspected Abuse/Neglect

Investigators may sometimes discover evidence of child abuse/neglect when they examine or interview pediatric research subjects or during data and sample collection activities in private residences (Resnik 2010c). All U.S. states have laws that mandate reporting of suspected child/abuse neglect to the local authorities (Administration for Children and Families. 2014). Some laws only mandate reporting for certain professions, such as physicians, nurses, or educators. North Carolina's child abuse statute requires any person or institution who suspects child abuse or neglect to report it to the department of social services. A person (or institution) who knowingly or wantonly fails to report suspected child abuse or neglect, or prevents someone else from reporting it, may be liable for a misdemeanor (North Carolina General Statutes 2013). Because children are vulnerable to harm or exploitation, there is little ethical controversy concerning the duty to report child abuse/neglect. When the department of social services receives a report of child abuse or neglect, it will conduct an investigation and may contact other authorities (such as the police) and take temporary custody of the child (or children). Since these actions can be very disruptive and stressful for the family, investigators and research staff should report child abuse/neglect only when they have a reasonable suspicion[8] that it has occurred, so that they do not cause families unnecessary harm. Researchers who work with children should have appropriate training and experience in recognizing the signs of child abuse or neglect, so that they can report it appropriately. They should also follow standard operating procedures for dealing with suspected child abuse or neglect and include information in consent and assent documents about mandated reporting when they are conducting research in which there is a reasonable chance they will obtain evidence of suspected abuse or neglect.

Investigators face similar issues when they discover evidence of abuse of elderly or disabled adults during examinations, interviews, or in-home visits. Most states also have laws mandating the reporting of abuse, neglect, or exploitation of elderly or disabled adults (Resnik 2010c). Because elderly or disabled adults may be more vulnerable to harm or exploitation than other adults, there is little ethical controversy concerning the duty to report abuse or neglect of these individuals. The main issue pertains to knowing how to identify signs of abuse or neglect. False reports of abuse

[7] In the law, credible evidence is evidence that is "worthy of belief; trustworthy (Black's Law Dictionary 2001:250)."

[8] In the law, reasonable suspicion is defined as a suspicion which is "supported by specific and articulable facts (Black's Law Dictionary 2001:584)."

or neglect can be stressful for caregivers and research subjects. Investigators and research staff should report abuse/neglect of older or disabled adults only when they have a reasonable suspicion that this has occurred. Researchers who work with older or disabled adults should have appropriate training and experience in recognizing the signs of abuse or neglect, so that they can report it appropriately. They should also follow standard operating procedures for dealing with suspected abuse or neglect of elderly or disabled research subjects.

6.7 Communicable Disease Reporting

Sometimes investigators perform tests on research subjects which may reveal that they have a communicable disease. Many states also have laws requiring health care professionals to report certain types of communicable diseases to public health authorities. For example, North Carolina requires health care professionals to report 73 different diseases to the Division of Public Health, including acquired immune deficiency syndrome (AIDS), human immunodeficiency virus (HIV), botulism, gonorrhea, hepatitis, influenza leading to death, Lyme disease, malaria, plague, Rocky Mountain spotted fever, syphilis, and yellow fever (North Carolina Administrative Code 2015a, b). Disclosures must include the person's name, address, and clinical and epidemiologic information. The Division of Public Health uses this information to conduct disease surveillance, investigate epidemics, and ask the infected person whom he or she has had contact with. For example, if a person is diagnosed with HIV/AIDS in North Carolina, public health authorities will ask him or her for the names of people he or she has had sexual relations with or used intravenous drugs with. They will then contact these sexual and drug partners and inform them that they have had contact with someone with HIV/AIDS (this procedure is known as contact tracing). They will also advise these partners to be tested for HIV.

Communicable disease reporting laws present investigators with a conflict between protecting confidentiality, respecting autonomy, and promoting trust on the one hand and obeying the law and protecting public health on the other. Since research subjects with communicable disease may infect other people and threaten public health, there is little controversy concerning the obligation to breach confidentiality to comply with communicable disease reporting laws. To avoid undermining subjects' trust, investigators should inform research participants who are being tested for reportable diseases about their obligations to report these diseases to the public health authorities. They should also inform them that the public health authorities will protect their confidentiality to the extent allowable under reporting laws. If subjects test positive for communicable diseases, investigators should inform them that they pose a risk to the public health and provide them with information about how to avoid transmitting those diseases. They should also provide them with a referral for treatment.

In some cases investigators may learn that subjects with communicable diseases do not intend to comply with procedures designed to protect the public health. For example, suppose a research subject with HIV admits that he does not intend to tell his wife and he plans to continue having unprotected sex with her. In many states and nations it is a crime for an HIV-infected person to knowingly have unprotected sex (Ahmed and Hull 2011). When an investigator learns that a research subject with HIV does not intend to take precautions to protect his or her sexual partners, the investigator must decide whether to inform those partners under the duty to warn rationale developed in the Tarasoff ruling. Investigators should use good judgment and balance conflicting moral values or principles in situations like these (Stanard and Hazler 1995). Normally, the investigator will be able to protect the subject's partners by making a report to the public health authorities, who will initiate contact tracing. However, an investigator might be concerned that further action is needed, such as contacting the police or informing the subject's partners about his HIV status. Since these other steps may badly damage the subject's trust, investigators should avoid them if at all possible. Instead, they should inform the subject about the risks he or she poses to his or her partners and encourage him or her to take reasonable precautions to avoid infecting them (Stanard and Hazler 1995).

6.8 Informing Family Members About Genetic Diseases

Genetic researchers sometimes acquire information that may be useful for promoting the health or well-being of subjects' family members. Researchers may acquire this information deliberately, i.e. when they are testing for genetic variants known or thought to be associated with particular diseases, or inadvertently, i.e. when they happen to discover such variants when they are testing for something else (see discussion of intended vs. incidental findings in Chap. 8). In either case, the researchers might feel that they have a duty to breach the subject's confidentiality to protect family members, who may also have the potentially harmful genetic variant (Dugan et al. 2003; Falk et al. 2003; Liao 2009). Consider the following hypothetical scenarios:

- During a study of the genetics of dementia, investigators discover that Tom, a 45-year-old male research subject, has tested positive for that gene that causes Huntington's disease, a progressive and incurable genetic condition involving degeneration of nerve cells in the brain. Onset of the illness typically occurs when a person is in his or her 40s. Victims develop dementia and lose control of their muscles. People who have only a single copy of the Huntington gene have nearly a 100% chance of developing disease (Mayo Clinic 2016). Tom has a wife and 22-year-old daughter. Investigators share the test result with Tom and he indicates that he does not want to tell his family members that he has the Huntington gene. Investigators are considering whether to share Tom's test result with his daughter, who may use this information to seek effective treatment (if it becomes available), prepare for the impact of the disease, or make reproductive choices (e.g. decide not to have children).

- During a study of the relationship between genetics, environment, and cancer, investigators discover that Marsha, a 35-year-old female, has tested positive for BRCA1 mutations. These mutations increase the risk of developing breast cancer by age 70 from 12% to 55–65% and ovarian cancer from 1.3% to 11–17% (National Cancer Institute 2015). Marsha's mother died from breast cancer at age 60. When Marsha learns her results, she says she does not want to share them with her 39-year-old sister or 55-year-old aunt, neither of whom have breast cancer. Investigators are considering whether to share this information the sister and aunt so they can be tested for BRCA1 mutations and take steps to reduce their risks of developing breast cancer or detecting it early (if they test positive).
- Investigators are conducting research on the genetics of heart disease among men and women without any evidence of heart disease by age 50. During the course of their investigation, they discover a gene that increases the risk of developing the disease to 57% for men and 44% for women. Men who are free from heart disease at age 50 normally have a 52% chance of developing this condition by age 95 and women have a 39% chance (Lloyd-Jones et al. 2006). They are planning to inform all the research subjects who test positive for this gene about their risks of increased risk of developing heart disease and they are considering whether to inform the subjects' family members, so they can be tested.
- Investigators are conducting a study on the relationship between genetics and cancer risk among agricultural workers exposed to pesticides. When analyzing the data after following the subjects for 10 years, the investigators discover a gene that increases the risk of a rare form of kidney cancer by 50%. The lifetime risk of developing this rare form of cancer is 1/10,000. They inform the human subjects with this gene that they have an increased risk of developing this rare disease and they advise them to inform their family members, so they can be tested.

These situations involve a conflict between protecting the subject's confidentiality and preventing harm to other people. Investigators might believe, following the Tarasoff reasoning discussed above, that they have a duty to inform affected[9] family members about the risks of harm they or their potential offspring face from having genetic predisposition for a disease and that this duty justifies breaching confidentiality (Keeling 2004). However, there are some important differences between these situations and the Tarasoff case that should make investigators reluctant to breach confidentiality.

First, none of these research subjects are intending to harm their family members. The potential harms are related to genetic variants the subjects may share with the family members, not the subjects' intentions or motives. Although the subjects' intent does not necessarily affect the risk of harm, it does impact his or her culpability, and one might argue that subjects who do not have malicious motives deserve greater confidentiality protections than those who do.

[9] By "affected" I mean family members who have a significant chance of having the genetic variant(s). For example, if a man has the Huntington gene, his daughter but not his wife would be affected. If a woman has BRCA1 mutations associated with increased cancer risk, he daughter(s), sister(s), grandmother(s), niece(s), aunt(s) and mother could all be affected.

Second, none of these situations involve the imminent risk of severe harm. Although all cases involve a risk of death and disease, these outcomes are not imminent. They may occur within years or decades, if at all.

Third, in the Huntington's case the harm is not currently preventable. Since there is currently no treatment for this disease, informing family members will not prevent them from developing the disease or halting its progression and may cause them needless stress. It may, however, help them to avoid passing the gene on to the next generation if they decide not to reproduce.

Fourth, in the last two cases, the probability of developing the disease as a result of the genetic predisposition is low. The heart disease gene is associated only with a 5% increased chance of developing the heart disease by age 95 for men or women. Also, numerous risk factors other than this gene, such as smoking, obesity, diabetes, poor diet, sedentary lifestyle, family history, and stress, can increase the risk of developing heart disease. While kidney cancer gene significantly increases the absolute probability of developing this disease by 50%, the relative probability is still quite low (1.5/10,000) because the disease is very rare.

Given these considerations, one could argue that the case for breaching confidentiality to share a subject's genetic test result with affected family members is strongest when the potential harms related to the genetic predisposition are: (a) severe, (b) highly probable, (c) imminent, and (d) preventable. None of these cases meet all four of these conditions, although the BRCA1 cases meet three of them (severity, probability, and preventability). Investigators who are considering breaching confidentiality should first inform research subjects about the risks affected family members face and encourage them to share their results with them before resorting to this option (Pate v. Threlkel 1995; Offit et al. 2004).

6.9 Conclusion

It is important for investigators to protect subjects' privacy and confidentiality to respect their autonomy, protect them from harm, and promote their trust. Investigators should inform subjects of the measures they will take to protect confidentiality and privacy. Potential threats to privacy and confidentiality are likely to continue to evolve in response to advance in science, technology, and statistics. For example, it may become much easier to identify individuals in databases and to sequence human DNA from bodily fluids or skin left in public places. Restricting access to genomic data and samples by means of DUAs and MTAs represents a workable compromise that protects privacy and confidentiality, promotes trust, and allows science to advance (Resnik 2010a). Only DNA sequence information that has been stripped of unique identifiers[10] should be published or placed on publicly available websites.

[10] For example, researcher could publish the sequence of a gene many people have in common but not sequences, such as single nucleotide polymorphisms, which can identify individuals.

Situations may sometimes arise when investigators have a duty to breach confidentiality to protect identifiable third parties or the public from harm. In some cases, investigators may be legally required to breach confidentiality so they can report suspected abuse/neglect or communicable diseases to government officials. Where appropriate, investigators should inform research subjects about their legal obligations under these reporting laws. They should use good judgment when deciding whether to go beyond what it legally required to protect individuals or the public from harm.

Chapter 7
Risks

In the previous two chapters, I applied the trust-based approach to ethical issues related to protecting human rights (i.e. autonomy and privacy) in research. In this chapter, I will shift the focus away from protection of rights toward the protection of welfare by examining issues related to managing risks to human research subjects.

As noted in Chap. 2, the federal regulations state that an IRB cannot approve a research study unless it determines that risks are minimized and reasonable in relation to expected benefits to the subject or society by means of the knowledge expected to be gained (Department of Health and Human Services 2009, 45 CFR 46.111). The regulations also require investigators to inform subjects about the reasonably foreseeable risks of the research (45 CFR 46.116a2). Other ethics guidelines include similar statements concerning the management and disclosure of risks (Council for the International Organizations of Medical Sciences 2002, 2016; World Medical Association 2013).

7.1 What Is Risk?

A risk is a chance of some harmful outcome, such as loss of life, property, or money. The degree of risk is a function of the probability and magnitude the harm. For example, a medical procedure with a 1% probability of death is much riskier than one with a 50% probability of a headache and no chance of death, because death is much worse than a headache (Levine 1988). Rid et al. (2010) have developed a seven-point scale for categorizing different types of harm associated with clinical research based on the duration and magnitude of the harm. The categories range from negligible (e.g. mild nausea) and small (e.g. headache), to severe (e.g. loss of a limb or paraplegia), and catastrophic (e.g. permanent, severe dementia or death).

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Since risk is partly a function of probability, it will be useful to distinguish between different types of probability estimates. A statistical probability is one based on the observed frequency of an event. For example, if one flips a coin 1000 times and it comes up heads 700 times, one might conclude that the probability of flipping the coin and getting heads is 70% + or − the standard error for this experiment (Weiss 2011). A mathematical probability is an estimate calculated by dividing the number of times a specified outcome can occur by total number of possible outcomes. For example, a mathematical estimate of the probability of flipping a coin and getting heads is 50%, since there is one specified outcome (heads) and two possible outcomes (heads, tails). A subjective probability estimate is a best guess that an outcome will occur. For example, one could place a bet on a horse race based on one's best guess that a particular horse will win. A best guess may be an educated guess, but we would still call it a subjective probability because it is not based objective data or mathematical relationships (Weiss 2011).

Some commentators have argued that we should avoid using subjective probability estimates in science and medicine, because subjective estimates can be biased by one's background beliefs, assumptions, values, and opinions (Earman 1992). If we are unable to objectively assess the probability that a negative outcome related to research will occur, and we do not want to use a subjective estimate, we could say that the negative outcome is a possible risk of research without assigning it a numerical estimate (Resnik 2013). If we think that a study may involve risks that we are not currently aware of, we could say that there may be some unknown risks related to the research.

7.2 Types of Risk Related to Research Participation

Risks related to research participation may include (Levine 1988):

- Medical risks, such as death, disability, injury, toxicity, nausea, shortness of breath, or adverse drug reactions;
- Psychological risks: such as pain, discomfort, distress, anxiety, remorse, shame;
- Social risks: such as discrimination, stigma, bias, identity theft;
- Financial risks: such as having to cover the costs of medical bills;
- Legal risks: such as liability for child support as a result of a paternity discovered during genetic testing.

7.3 Risk and Trust

Risks that materialize can negatively impact subjects' and community's trust in investigators, institutions, and IRBs, since subjects expect to be protected from harm (Richardson and Belsky 2004; Miller and Weijer 2006). Risks that materialize

can also undermine the public's trust in the scientific enterprise. Harm to human subjects can be especially detrimental to trust when it occurs to healthy volunteers enrolled in research, since it is not expected (Resnik 2012c). A research subject with terminal liver cancer, for example, may expect to become very ill or even die as a result of participating in a clinical trial. If the subject dies, his or her family may regard the outcome as regrettable but not unexpected. They may regard the subject's decision to participate in the study as a reasonable choice, given his poor prognosis, because the study offered him the prospect of treatment (Wendler and Miller 2008b). If a healthy volunteer dies in a research study, however, surviving family or community members, and the public at large may react very negatively to this outcome, because it was unexpected. Jesse Gelsinger's death in a Phase I trial (discussed in Chap. 2) significantly damaged public's trust in the institution and gene therapy research because he was relatively healthy and not expected to derive any significant medical benefits from participation in the experiment (Yarborough and Sharp 2009; Resnik 2012c). If Gelsinger had not died in the experiment, the other problems with study, such as undisclosed risks and conflicts of interest and lax adverse event reporting, may have appeared to be less serious. Because he died, however, these problems became magnified in the minds of the public, federal agencies, and ethicists (Yarborough and Sharp 2009). Likewise, Ellen Roche's death (discussed in Chap. 2) in an asthma study drew intense scrutiny and criticism because she was a healthy volunteer (Resnik 2012c).

Harms other than adverse health outcomes can also negatively impact trust. In the Havasupai case (discussed in Chap. 2) the subjects were not physically injured, but they may have suffered psychological harm as a result of what they perceived as a misuse of their blood samples. Likewise, community members may have felt violated by what they regarded as a betrayal of trust. In the Milgram experiment (discussed in Chap. 2) some of the subjects experienced distress after learning that they were willing to administer dangerous electric shocks to their comrades. A data security breach could cause subjects psychological distress, even if they never experience any other adverse consequences, such as discrimination or identity theft (see discussion of the University of North Carolina case in Chap. 6).

Thus, proper management of risks is very important for maintaining and promoting trust in research with human subjects. Below we shall consider some of the implications of promoting trust for ethical and policy issues related to research risks.

7.4 Assessing Risk

In making decisions concerning the management of research risks, the IRB must assess the risks of the research, so that it can determine whether the risks are reasonable in relation to the benefits (Wendler and Miller 2008b). Risk assessment consists of three distinct processes: (1) risk identification (i.e. listing or describing risks), (2) risk estimation (assigning probabilities to risks), and (3) risk evaluation (i.e. making a judgment concerning the degree of harm pertaining to risks) (Shrader-Frechette

1991). The research proposal submitted by the investigator should provide the IRB with the information it requires to assess risks. If the proposal does not include this information, the IRB may table it and send it back to the investigator with a request for more risk information. The IRB may also consult with outside experts concerning the risks of the study or conducted its own literature review. As noted above, it may not always be possible to obtain objective probability estimates of risk, due to lack of evidence, and there may be some risks which are not known.

While risk identification and risk estimation are scientific judgments informed by empirical data, risk evaluation is a type of moral judgment, since it requires the IRB to assign a value or worth to different outcomes (Kimmelman 2004; Rid et al. 2010; Rid and Wendler 2011). For example, suppose that the IRB is reviewing a study on healthy volunteers and the main risks of the study are associated with a bronchoscopy that will be performed on the subjects. The main risks of the bronchoscopy are coughing, discomfort, chest pain, bleeding, and in rare cases, pneumothorax, i.e. air between the lungs and chest wall (National Heart, Lung, and Blood Institute 2016a, b). The IRB must decide whether the benefits of the study (e.g. the knowledge gained) justify the risks of the bronchoscopy. To make this judgment, the IRB must have some way of comparing the positive worth of the benefits to the negative worth of the risks related to the bronchoscopy.

In making risk assessments, IRBs should distinguish between the risks of the research and the risks of the clinical care that the patients/subjects would receive even if they were not participating in research (Wendler and Miller 2007, 2008b). For example, consider a hypothetical study whose goal is to determine whether genetic factors impact tolerance for a kidney transplant. The study enrolls patients who are receiving a kidney transplant. The investigators collect an additional 50 ml of blood when blood is being drawn for clinical testing. The investigators perform genetic analyses on DNA extracted from the blood and correlate their findings with patient outcomes. The main risk of this research would be the risk of collecting an additional 50 ml of blood, not the risk of the kidney transplant, since the patients are receiving the transplant as part of their clinical care.

Risk assessment should also consider the net risks of all the study activities (see Table 7.1). For example, suppose a pulmonary function study includes: a medical history and exam; 30 ml blood draw once a week for 6 weeks, urine sample collection once a week for 6 weeks; sputum sample collection once week for 6 weeks; pulmonary function testing once every 6 weeks; two chest x-rays (radiation dose equivalent to 20 days of normal background radiation); and two bronchoscopies with conscious sedation at week 2 and week 6. The risks of this study would be the risks of all study activities combined (Wendler and Miller 2007, 2008b).

Table 7.1 Estimated risks associated with some research procedures*

Procedure	SAE** risk	Mortality risk
Blood donation, 50 ml, healthy adult	Negligible	Negligible
Blood donation, 550 ml unit, healthy adult[a]	2/1000	Negligible
Physical examination	Negligible	Negligible
Survey or interview	Negligible	Negligible
Electrocardiogram	Negligible	Negligible
Magnetic resonance imaging without contrast agent	Negligible	Negligible
Magnetic resonance imaging with contrast agent[b]	7.5/100,000	1/1 million
Chest x-ray[c]	Negligible	Negligible***
Dual-energy x-ray absorptiometry (DEXA) scan[d]	Negligible	Negligible***
Computerized tomography scan[e]	Negligible	Negligible***
Skin or muscle biopsy[f]	Negligible	Negligible
Glucose tolerance test[g]	Negligible	Negligible
Allergy skin testing[h]	1/100,000	1/2 million
Cytapheresis[i]	4/1000	1/2 million
Lumbar puncture, healthy adult[j]	1.5/100	1/1 million
General anesthesia[k]	8/100	1/100,000
Pharmacokinetic or drug dosing study[l]	6.4/1000	1/100,000
Cardiac stress testing[m]	9/10,000	5/100,000
Diagnostic upper endoscopy[n]	2/1000	10/100,000
Diagnostic colonoscopy[o]	2.5/1000	20/100,000
Bronchoscopy[p]	5/1000	20/100,000
Cardiac catheterization[q]	3.54/100	110/100,000

*Risks are general estimates based on available data. Individual risks may vary, depending on age and health status

***SAE* Serious adverse event, i.e. an event that is life-threatening or results in death, hospitalization, permanent damage of disability, or congenital/birth defect

***Exposure to ionizing radiation may increase lifetime cancer risk, depending dose, and frequency and age of exposure

***Risks may be lower in healthy individuals

[a]Crocco and D'Elia (2007);[b]Schmidt et al. (2011);[c]X-Ray Risk (2016);[d]X-Ray Risk (2016);[e]X-Ray Risk (2016);[f]Wang et al. (2011);[g]National Health and Nutrition Examination Survey (2007);[h]Bernstein et al. (2004);[i]Crocco et al. (2009);[j]Evans (1998) and Thomas et al. (2000);[k]Li et al. (2009), Jenkins and Baker (2003). The SAE rate for general anesthesia is relatively high because many of the complications that occur during anesthesia, such as compromised airway or cardiac arrhythmia, are life-threatening;[l]Emanuel et al. (2015) and Shah et al. (2004);[m]Stuart and Ellestad (1980);[n]Froehlich et al. (1999);[o]Froehlich et al. (1999);[p]Surratt et al. (1976), Pue and Pacht (1995), and Stahl et al. (2015);[q]Tavris et al. (2007)

7.5 Minimizing Risk

Managing risks also includes deciding whether the study includes appropriate measures to minimize risks (Wendler and Miller 2008b). The measures used to minimize risk depend on the aims of the study and target population as well as the

research procedures, methods, tests, and interventions. Some measures used to minimize risk include:

- Conducting a review of the published literature (including animal and human studies) related to the research to better understand the risks;
- For Phase I studies involving dosing, beginning the dosing at a low level and gradually escalating the dose, depending on the subjects' tolerance for the drug or biologic;
- For Phase I studies involving medical dosing of novel drugs or biologics, begin the study by dosing only a few subjects and then expand subject pool when it is safe to do so;
- For studies involving the administration of drugs, obtaining a medical history from the subject to find out whether they have any known medication allergies;
- Excluding research subjects from the study who may be at increased risk due to their medical condition, concurrent or recent enrollment in another study, pregnancy status, age, etc.;
- Carefully monitoring subjects when they are in the study and following up with them after they have completed the study;
- For clinical trials, using a data and safety monitoring board (DSMB) to evaluate preliminary data from the study and determine whether the study should be modified or stopped to protect subjects from harm;
- Reporting unanticipated problems, non-compliance, adverse events to the IRB, institution, and sponsor in a timely fashion;
- For studies involving radiation, consulting with a radiation safety committee to protect subjects from unnecessary exposures to radiation;
- For studies involving medications, following appropriate guidelines for dosing and administration;
- For studies involving the collection of blood, taking no more blood than is necessary to achieve the study's aims and not taking too much blood during during a particular period (e.g. no more than 550 ml of blood per 8 weeks in healthy adults)[1];
- For studies involving biopsies, take no more tissue than is required to achieve the study's aims with appropriate wound care;
- For studies involving magnetic resonance imaging, ensuring that subjects have no metal on the body which could be attracted to the magnet;
- For studies involving medical procedures that require sedation, ensuring that subjects follow proper safeguards (such as not eating or taking certain types of medications prior to sedation);
- For studies which ask subjects questions about stressful events they have experienced, such as trauma, sexual abuse, and physical abuse, making counseling services available for subjects who experience distress;

[1] National Institutes of Health (2009).

- For all types of research, ensuring that investigators and staff have the appropriate experience, knowledge, and training to perform study procedures safely and effectively;
- For all types of research, developing and following standard operating procedures (SOPs) for performing interventions, procedures, and tests.
- For all types of research, implementing procedures to protect privacy and confidentiality.

As one can see from this list, there are many ways of minimizing the risks of research. The list is but a small sample of the types of measures that investigators might use to protect subjects from harm.

7.6 Minimal Risk

The concept of minimal risk plays an important role in the federal research regulations. First, members of the National Commission (1979) recognized that children and other vulnerable subjects should have additional protections from harm or exploitation, because they have a limited ability to protect themselves.[2] However, the members of the Commission also recognized that vulnerable subjects should be allowed to participate in some types of low-risk research that does not offer direct benefits, because this research can benefit society without imposing significant risks on the participants. The concept of minimal risk emerged from the Commission's discussions as threshold for allowable types of research that does not benefit vulnerable subjects (Freedman et al. 1993; Wendler et al. 2005). Minimal risk plays a key role in defining approvable categories of research for vulnerable subjects under Subparts B, C, and D of the Common Rule. An IRB can approve research that does not offer direct benefits to children when the risks are minimal (45 CFR 46.404) or they are a minor increase over minimal and the study is "likely to yield generalizable knowledge about the subject's disorder or condition (46.406)." An IRB can approve research that does not offer direct benefits to a pregnant woman or her fetus if the risks to fetus are minimal (46.204), and an IRB can approve research that does not offer direct benefits to prisoners if the risks are minimal (46.306). Additionally, an IRB can waive informed consent requirements for minimal risk research (45 CFR 46.116d).[3]

Second, the members of the National Commission (1979) also recognized that not all low-risk research activities need to be reviewed by the full IRB. The rationale for this position was that the level of review should be proportional to the risks involved in the research (Hunter 2007). The revisions to the Common Rule also reflect this thinking (Department of Homeland Security et al. 2017; see Chap. 11).

[2] These additional protections could be viewed as a form of soft paternalism. See discussion in Chap. 2.

[3] In Chap. 9 I will discuss research with vulnerable subjects in more depth.

Minimal risks functions as a threshold test for deciding whether research requires full IRB review. The Common Rule describes an expedited review procedure which allows the IRB Chair or a designated IRB member to approve minimal risk (46.110). In reviewing minimal risk research, the Chair or designee shall apply the review criteria set forth in 45 CFR 46.111 to the proposed study. The Chair or designee cannot disapprove minimal risk research; only the full IRB can disapprove reach (45 CFR 46.110).

As noted in Chap. 2, the federal regulations define minimal risk minimal risk in terms of the risks of daily life or the risks of routine physical or psychological examinations or tests (45 CFR 46.102i). An IRB can use either of these parts of the definition for making decisions concerning the oversight of research. For example, if the main risk of a study is a venipuncture, the IRB could decide whether this risk is minimal by comparing it to the risk of having blood drawn as part of routine medical testing. If the research procedures, methods, tests, or interventions used in a study do not resemble routine physical or psychological examinations or tests, the IRB can decide whether the study is minimal risk by comparing its risk to the risks of daily life (Wendler et al. 2005). For example, if a behavioral study involves deception, an IRB would need to compare the risks of deception to the risks of daily life, since routine psychological tests do not involve deception.

Research has shown that IRBs interpret minimal risk differently. Shah et al. (2004) surveyed 188 IRB chairs concerning eleven different procedures conducted on healthy 11-year-old children. 48% classified a magnetic resonance imaging scan with no sedation as minimal risk, while 35% classified it as a minor increase over minimal risk, 9% said it was more than a minor increase over minimal risk, and 8% said they were unable to determine the risk. 23% classified allergy skin testing as minimal risk, 43% classified it as a minor increase over minimal risk, 27% classified it as more than a minor increase over minimal risk, and 17% said they were unable to determine the risk (Shah et al. 2004). Green et al. (2006) found significant variation in IRB risk classifications of the same study reviewed at 43 different research sites. 31 IRBs judged the study to be more than minimal risk, while 10 classified it as minimal risk, 1 said it was exempt from IRB review, and another disapproved the study as too risky.

Different interpretations of minimal risk in pediatric research may result in unequal treatment of human subjects, which is an ethical concern (Resnik 2015c). According to the formal principle of justice, people who are equal (in relevant ways) should be treated equally (Rawls 1971; National Commission 1979). For example, if two people perform the same job and have similar experience and talents, they should receive the same pay. Paying one person more money based on an irrelevant characteristic, such as gender or race, would violate the formal principle of justice. The equal protection clause of the 14th Amendment to the U.S. Constitution (1789), which holds that states shall provide people with equal protection under the law, provides legal affirmation of the moral idea that equals should be treated equally. Variations in the interpretation of minimal risk can violate the formal principle of justice because the same pediatric study might be approved by an IRB that classifies it as minimal risk but disapproved by one that classifies it as more than minimal risk.

Thus, one IRB would allow children to be exposed risks in research that another IRB would not permit. This predicament would lead to unequal protection for children involved in research.

To address concerns about variation in the interpretation of minimal risk, the Office of Human Research Protections (OHRP) has provided guidance on categories of research that can be reviewed through an expedited procedure (Office of Human Research Protections 1998). Although this document does not instruct IRBs on how to interpret minimal risk, it does provide some guidance concerning applying the concept of minimal risk to expedited review. According to OHRP, some types of research procedures that can be reviewed by an expedited procedure include (Office of Human Research Protections 1998):

- Collection of blood from a healthy, non-pregnant subject weighing at least 110 pounds; the total amount collected cannot be more than 550 ml per 8-week period and no more than two times per week;
- Collection of blood from children, no more than 50 ml or 3 ml per kg (whichever is less) in an 8-week period and no more than two times per week;
- Collection of biological specimens (such as hair, toenails, cheek scrapings, sputum) by non-invasive means;
- Surveys, interviews, focus groups, oral history;
- Continuing review of research where the study is closed for enrollment and the remaining research activities are limited to long-term follow-up or data analysis

It is worth noting that OHRP has not updated this list since 1998. The revisions to the Common Rule require OHRP to update this list more frequently (Department of Homeland Security et al. 2017).

While this list of procedures provides some guidance for interpreting the phrase "routine physiological or psychological examinations or tests" it does not provide any guidance on interpreting the concept of daily life risks. Two different interpretations of this concept have emerged in the literature: a relativistic interpretation and an absolutist interpretation (Resnik 2005a; Wendler et al. 2005). According to the relativistic interpretation, the risks of daily life are the risks typically encountered by the population being studied (Freedman et al. 1993). Some have objected to this interpretation because it could allow children who are already facing significant risks to be exposed to greater risks in research than those who do not face these risks, which would be unjust, because it would involve an unfair distribution of the benefits and burdens of research and violate the formal principle of justice (Kopelman 1981; National Bioethics Advisory Commission 2001a; Resnik 2005a). For example, if investigators are conducting a study on children living in a poor neighborhood in Baltimore, MD, the risks of daily life would be the risks typically encountered by those children, which might include significant hazards, such as street violence, gunfire, riots, and so on. If the same study is conducted in an affluent neighborhood in Bridgeport, CT, the risks of daily life would not include these risks. The same study might approvable in Baltimore but not in Bridgeport, if one follows the relativistic interpretation of minimal risk (Resnik 2005a).

Table 7.2 Some daily life risks*, U.S. Population[a]

	One year risk of death	Lifetime risk of death
Accidents (all types)	1/2372	1/30
Suicide	1/7533	1/96
Motor vehicle accident	1/8826	1/112
Assault by firearm	1/28,153	1/358
Fire/smoke inhalation	1/113,471	1/1442
Falling on stairs/steps	1/148,306	1/1884
Drowning in a swimming pool	1/477,902	1/6072
Accidental firearms discharge	1/527,228	1/6699
Natural disaster**	1/530,822	1/6736
Flying	1/630,753	1/8015
Falling from a ladder or scaffolding	1/670,090	1/8514

*Does not include disease risks

**Includes hurricanes, tornados, floods, earthquakes, lighting, blizzards, and dust storms

[a]Data from the Insurance Information Institute (2016)

Commentators have defended the absolutist interpretation of minimal risk on the grounds that it does not allow children living in areas exposed to high risks to be treated differently in research and therefore is more just (or fair) than the relativistic interpretation. According to the absolutist interpretation, the risks of daily life should be those typically encountered by the average healthy child (for pediatric research) or the average healthy adult (for non-pediatric research) (National Bioethics Advisory Commission 2001a; Wendler et al. 2005). Wendler et al. (2005) have attempted to quantify the risks typically encountered by the average healthy child living in the U.S. by estimating the risks associated with activities that children often engage in, such as bicycling, sports, swimming, and riding in automobiles. (See Table 7.2 for U.S. daily life risks.)

One problem with the absolutist interpretation of minimal risk is that it is difficult to define the risks typically encountered by the average healthy child or adult, since risks may vary a great deal by where one lives (Binik 2014). Wendler et al. (2005) focus on the risks typically encountered by children living in the U.S., but children living in other countries might typically encounter greater or lesser risks than those living in the U.S. Should our benchmark be the daily life risks typically encountered in a particular country? If we follow this line of thinking, how should we deal with an international collaborative research projects in which children typically encounter different risks in different countries? Should we use the U.S. standard of minimal risk or the standard within the host country? To resolve conflicts related to international research collaborations, we would need to use a standard that transcends any particular country or geographic region, e.g. risks typically encountered by average healthy child or adult living on the planet Earth. But it is difficult to conceive of how we would identify or quantify these risks, since we would need to compile and analyze data from all over the world. Thus, proponents

of the absolutist standard may need to concede that minimal risk needs to be benchmarked to a particular country.

Looking beyond the particularities at issue in the debate about how to interpret the concept of minimal risk in research, we can see that this debate involves, at a more fundamental level, a conflict between protecting human subjects from harm and advancing scientific research (Freedman et al. 1993; Kopelman 2000). Relativistic definitions of minimal risk may allow studies to take place that would not be approvable under absolutist definitions. Absolutist definitions may provide greater protection for human subjects but at the expense of thwarting socially valuable research (Binik 2014). Thus, the minimal risk debate boils down to a conflict between two ethical principles: non-maleficence vs. beneficence. The members of the National Commission (1979) recognized this conflict and developed the concept of minimal risk to deal with it. But, as we have seen, the concept of minimal risk does not completely resolve the underlying moral conflict (Binik 2014).

If we think about this debate from the perspective of trust, we should ask ourselves which approach to interpreting minimal risk is most likely to promote trust. As noted above, research subjects trust investigators, institutions, and IRBs to protect them from harm. If subjects who are harmed discover that an IRB has approved a study as minimal risk, then this may damage trust in the IRB, institution, and investigators. Although studies involving only minimal risk are not likely to cause serious harm to research subjects, harm—and especially the perception of harm—can still occur in this research. For example, the Johns Hopkins IRB classified the Kennedy Krieger study (discussed in Chap. 2) as minimal risk but the Maryland Supreme Court found that the study was more than minimal risk (Mastroianni and Kahn 2002). The parents of two of the children in the study sued the institution and the investigators because they believed that the research exposed their children to the risks of lead exposure, even though they were already living in homes with lead paint. Likewise, three IRBs classified the CHEERS study (discussed Chap. 2) as minimal risk. Although the study was never implemented, critics argued that the study would expose children to the risks of pesticide exposure, although the protocol did not require parents to use pesticides (Resnik and Wing 2007). Additionally, SUPPORT study investigators (see discussion in Chap. 1) argued that their research was minimal risk (Rich et al. 2012). But critics claimed that the study was more than minimal risk and that parents were not properly informed of the risks.

There are several lessons one can draw from these cases. First, investigators, institutions, and IRBs should carefully consider how to best protect vulnerable subjects in minimal risk research that has no prospect of direct benefit to participants. If there is a dispute concerning a study's risk classification, investigators and IRBs should explore ways of further reducing risk so that it will clearly meet the minimal risk standard. Second, even if there is scant evidence that subjects have been significantly harmed in minimal risk research, subjects (or their representatives) may nevertheless sometimes perceive that harm has occurred. When it comes to promoting trust, perceptions can matter a great deal, since trust is often based on the perception of fidelity or integrity. Although it is not realistic to expect that investigators, institutions, or IRBs can prevent adverse perceptions from occurring, they should

nevertheless take steps to minimize the perception of harm by gauging the community's attitudes toward risk. For example, community members who serve on the IRB could share their knowledge of the community's attitudes toward risk with the board when it is trying to determine whether a study should be classified as minimal risk. If the board understands "daily life risks" to mean the daily life risks of a typical child in the U.S., it could adjust this standard to accommodate local sensibilities.

7.7 Research on Healthy Volunteers

Healthy volunteers participate in a variety of studies, ranging from low-risk social/behavioral, epidemiological, or sample collection studies to riskier ones involving intentional exposures to environmental agents (such as air pollution or industrial chemicals) or drugs/biologics (e.g. Phase I trials) (Resnik 2007d, 2012a, c).[4] The federal research regulations place no limits on the risks that healthy, adult volunteers may be exposed to in research; they only require that risks be reasonable in relation to expected benefits (45 CFR 46.111). Although healthy volunteers do not receive direct benefits from participation, such as medical treatment, they may receive indirect benefits. For example, a study might provide a subject with useful health information, such as data concerning his or her blood pressure, cardiac function, blood sugar levels, genetic susceptibilities, and so on. Additionally, healthy volunteers may derive some sense of self-worth from knowing that they have made a contribution to the advancement of science (National Bioethics Advisory Commission 1998). Although most volunteers also consider money they receive from participation as a benefit, federal agency guidance discourages IRBs from treating financial compensation as benefit in its risk/benefit calculus (Wertheimer 2011). Thus, when IRBs consider whether risks for healthy volunteers are reasonable in relation to benefits, they must focus, for the most part, on the benefits of the research for society (Miller and Joffe 2009; Resnik 2007d, 2012c).

Healthy volunteers sometimes experience significant harm in research. For example, notable deaths of healthy volunteers in research include Ellen Roche in Johns Hopkins's asthma study and six subjects in Walter Reed's yellow fever experiments (see discussion in Chap. 2). In 2006, six healthy volunteers participating in a Phase I trial of a monoclonal antibody (known as TGN1412) conducted by Paraxel at Northwick Park and St. Mark's Hospital, London were hospitalized after they developed immune responses that led to multiple organ dysfunction (Goodyear 2006). In 2016, six healthy volunteers in a Phase I trial of medication intended to treat mood disorders and motor neuron dysfunction conducted in Rennes, France by

[4] The National Institute of Environmental Health Sciences and the Environmental Protection Agency conduct studies that expose healthy volunteers to air pollution. The purpose of this research is to better understand how pollutants affect the human respiratory system. See Resnik (2007a, b, c, d, 2012b).

Biotrial were hospitalized for adverse drug reactions. One of the volunteers was pronounced brain-dead and three of them may have suffered permanent brain damage. 84 previous subjects who had received the medication did not develop significant adverse reactions (Chan 2016).

Although serious harm to healthy volunteers participating in research is rare, it does occur. Emanuel et al. (2015) conducted a meta-analysis of adverse events in 431 non-oncology Phase I studies conducted between 2004 and 2011 at Pfizer test sites in Belgium, Singapore, and the U.S. They found that 7028 subjects (63.7%) experienced adverse events, while 4000 (36.3%) did not. 84.6% of adverse events were mild, 14.4% were moderate, 1% were serious, and 0.31% were severe. The investigators defined a serious adverse event (SAE) as an event involving death, a life-threatening condition, hospitalization, disability of permanent damage, or a congenital abnormality or birth defect. No subjects died in the studies the researchers examined (Emanuel et al. 2015).

The prospect of serious harm to healthy volunteers raises the issue of whether there should be any limits on the risks they are permitted to face in research (Miller and Joffe 2009; Resnik 2012c). The only research ethics guideline that mentions limitations on risks for healthy volunteers is the Nuremberg Code (1949), which states that: "No experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects." This guidance is not very useful, however, because it does not define "a priori reason" and it would probably prohibit most oncology clinical trials in which research participants must face the risk of a serious adverse event but also have the opportunity to receive effective treatment for their disease (Resnik 2012c).

The issue of whether to limit the risks that healthy, adult volunteers can face in research involves a conflict between respect for dignity/autonomy and beneficence on the one hand and non-maleficence on the other. Respect for dignity/autonomy and beneficence justify the position that there should be no limitations on the risks that healthy adults can face in research. Healthy adults, one might argue, should be allowed to make decisions concerning their risk exposure without outside interference. If we respect healthy adults' decisions to engage in risky occupations (see Table 7.3 for occupational risk data) and hazardous recreational activities (such as smoking, skydiving, etc.) we should also respect their informed decisions to participate in risky research (Miller and Wertheimer 2007). Furthermore, participation in risky research can benefit society in many ways. The yellow fever experiments, for example, provided public health and government officials with information which was essential to controlling the disease (i.e. that the *Aedes aegypti* mosquito was the disease vector). Phase I studies play a crucial role in the development of new drugs and biologics, and environmental exposure studies can provide us with important data pertaining to the regulation of pollutants and chemicals (Resnik 2012a).

The principle of non-maleficence supports the position that there should be some limits on the risks that healthy adults can take in research. We enact many different policies to that protect healthy adults from exposures to risks, such as laws pertaining to seatbelt and motorcycle helmet use, food and drug safety, workplace safety,

Table 7.3 U.S. Occupations, ranked by mortality risk[a]

Occupation	Annual deaths per 100,000
Fishermen	131.52
Loggers	97.05
Airplane pilots	69.53
Extraction workers (mining, oil, natural gas)	56.79
Iron and steel workers	42.61
Roofers	36.26
Garbage collectors	33.16
Farmers and ranchers	24.04
Truck drivers	24.03
Power line workers	22.85
Agricultural workers	20.48
Construction workers	18.76
Taxi drivers and chauffeurs	17.85
Police officers	15.96
Maintenance/repair workers	15.78
Landscapers	14.59
Industrial machinery workers	11.81
Athletes, coaches, and umpires	10.97
Retail sales managers	3.19
Scientists	1.83
Personal care workers	1.45
Community and social service workers	1.28
Retail sales workers	1.27
Food preparers	1.04
Office administrators	0.56

[a]United States Bureau of Labor Statistics (2015)

and so on. The reasoning that justifies prohibitions on selling or possessing cocaine, methamphetamine, and other dangerous drugs, also justifies preventing healthy adults from participating in experiments that society deems to be too risky (Resnik 2012c). While these policies are paternalistic (see discussion in Chap. 2), one might argue that they are needed to protect people from harm.

If we think of this issue from the perspective of trust, catastrophic harms to human subjects (such as death) can significantly undermine the public's trust in the research enterprise (Resnik 2012c). The deaths of Gelsinger and Roche elicited a negative public reaction, as did the disastrous Phase I trials conducted by Paraxel and Biotrial. One could argue that some limits on the risks that healthy volunteers can face in research are necessary not only to protect individuals from harm but also to protect the scientific enterprise (Miller and Wertheimer 2007; Resnik 2012c, 2015b).

Assuming that some limits on the risks that healthy volunteers can face in research can be morally justified, the next issue to address is establishing an acceptable risk level (Resnik 2012c). The concept of minimal risk, as we saw earlier, provides a threshold for acceptable risk in some categories of vulnerable subjects. Perhaps we can develop a concept of "maximum" risk for risk management at the other end of the spectrum. If we think of research participation by healthy volunteers as a type of paid labor in which people are asked to take some risks, we can compare it to other forms of labor in which people face some risks (see Table 7.3). People who work on fishing boats face the highest occupational mortality risks, with 131.52 deaths per 100,000, while people who do administrative work in offices are at the low end of the range, with 0.56 deaths per 100,000. One could argue that a maximal risk threshold for healthy volunteers should fall somewhere between these two extremes, e.g. 65 deaths expected per 100,000. Thus, a bronchoscopy (see Table 7.1) would be an acceptable procedure to perform on a healthy volunteer since the risk of death is 50 per 100,000 but a cardiac catheterization would not be because the risk of death exceeds the limit at 110 per 100,000. Also, risky activities often produce adverse effects that are less catastrophic than death but which are still serious. To set a maximum level for these risks, we could estimate that 1/200 SAEs would result in death, so a maximum level of expected SAEs would be 65/100,000 × 200 = 65/500 or 1.3%. For the sake of simplicity, we could round this number down to 1%. Thus, I propose the following standard:

Maximum level of risk for healthy adult volunteers participating in research: Risk of a serious adverse event is not greater than 1% and the risk of death is not greater than 65/100,000 (0.065%).

Now, one might object that the maximum level of risk is arbitrary. Why not set it higher or lower? I agree that the choosing an exact number is somewhat arbitrary but it does reflect risk exposure that falls within the realm of social acceptability, since it is based on occupational risk data. If we set the level much higher, then more subjects could suffer significant harms in research, which would have negative repercussions for the injured parties and the scientific enterprise. If we set the maximum level much lower, then we would prohibit investigators from conducting important research that benefits society. London (2006), for example, argues that the maximum risk level should be equivalent to the risks that voluntary firefighters face, or 3.4 deaths per 100,000. Setting the level this low, however, would not allow investigators to perform cardiac stress tests or bronchoscopies on healthy volunteers, which would prevent investigators from obtaining important health information. Some studies of how air pollution impacts lung function include cardiac stress tests and bronchoscopies (Resnik 2012a).

One might also object that the maximum level is too rigid. Situations might arise in which it would be desirable to exceed this risk level to conduct research with important benefits for society. I agree that the maximum risk level should not be rigid: it should be a guideline, not an absolute rule. An IRB should be able to approve a study that exceeds this risk level if it determines that the research addresses a compelling societal need.

7.8 Phase I Trials on Patients

Risk management pertaining to research involving patients is very different from risk management involving healthy volunteers because patients may benefit from their participation. We allow studies to be performed on patients that we would consider to be too risky to perform on healthy volunteers because patients may gain access to beneficial treatment (Wendler and Miller 2008b). If someone has a 90% chance of dying from terminal cancer in the next 3 months when treated with conventional therapy, then it may be reasonable for them to participate in clinical trial of an experimental drug with a 50% chance of killing them but also a 50% chance of curing them, since a 50% chance at a cure is better than a 10% chance.

Although clinical research studies may offer patients direct benefits, their main purpose is to develop new knowledge. Clinical trials are designed to evaluate medical treatments, not to provide individualized care for patients. It is important for investigators to help their patients understand the difference between research and therapy and not take advantage of their desperate situation (see discussion of the therapeutic misconception in Chap. 4). Patients with a terminal or incurable illness may be willing to try anything that gives them a chance to obtain effective treatment.

Although Phase I clinical trials are usually performed on healthy volunteers, some Phase I studies are performed on patients with terminal or incurable diseases (such as some types of cancer). The rationale for conducting Phase I studies on sick patients is that the treatments are so dangerous (e.g. intensive chemotherapy) that it would be unethical to ask healthy volunteers to receive them. Patients with terminal or incurable illnesses have nothing to lose and much to gain by trying experimental treatments in Phase I studies (Agrawal and Emanuel 2003, 2008). Jesse Gelsinger (see discussion in Chap. 2) was one of these patients.

Some have argued that most Phase I oncology trials are unethical because the risks are not reasonable in relation to expected benefits since the patients' chances of benefit are remote (Miller 2000). Phase I trials are designed to evaluate safety and toxicity, not efficacy. These studies often systematically escalate dosing to determine the maximum tolerable dose. Patients may therefore not receive a dose that is effective at treating their disease. Also, Phase I studies usually last 30 days or less, which may not be enough time for patients to derive significant or long-lasting benefits (Miller 2000).

Others have argued that the risks of Phase I trials on sick patients are justifiable if there is a reasonable expectation of direct benefit for the patient (Agrawal and Emanuel 2003, 2008). Studies have shown that the overall response rate in Phase I oncology trials is 4.4%. The risks of these studies are reasonable, given this population, with a morality rate due to toxicity around 0.5% (Agrawal and Emanuel 2008). Readers will note this morality rate of 5 deaths per 1000 subjects far exceeds that maximum mortality rate for healthy volunteers defended above, i.e. 65 deaths per 100,000.

In thinking about Phase I trials on sick patients from the perspective of trust, informed consent is a key consideration (King 2000). Patients with a terminal or incurable illness may be especially susceptible to the therapeutic misconception,

since they may be willing to try anything that will give them a hope of a cure (Miller 2000). Investigators who enroll patients in Phase I trials should carefully explain to them the risks and benefits of the research as compared to standard treatment if any is available. Some cancer patients may prefer to forego treatment and live the remainder of their days with fewer adverse effects and symptoms than to undergo an intensive chemotherapy regimen that does not significantly increase their lifespan but causes significant suffering. Investigators who do not clearly discuss the different options (including the option of no treatment) with their oncology patients may betray their trust.

7.9 Randomized Controlled Trials

Many types of clinical trials randomly allocate patients to different treatment groups to minimize bias due to treatment assignment. For example, selecting the healthiest patients to receive a medication could bias the outcome in favor of that medication. The randomized controlled trial (RCT) has become the "gold standard" for clinical research that aims to evaluate medical interventions with respect to safety and efficacy (Sackett et al. 1997). The SUPPORT study and the HIV prevention trials (discussed in Chap. 1) were RCTs.

Some physicians and ethicists have argued that randomization is morally dubious because it conflicts with the physician's obligation to provide the best treatment for his or her patients (Fried 1974; Marquis 1983; Hellman and Hellman 1991; Rothman and Michels 1994). In clinical practice, physicians recommend treatment based on their medical knowledge, the patient's condition, and the patient's preferences. For example, if a woman has breast cancer, a physician could recommend various treatment options, such as mastectomy, lumpectomy, different types of chemotherapy, and radiation. The woman's treatment decision should not be made at random, but should depend on various factors, such as the size and stage of the tumor, her ability to tolerate different types of chemotherapy, her concerns about disfigurement, etc.

Fried (1974), Freedman (1987), Miller and Weijer (2003) and others have developed the concept of clinical equipoise to justify random assignment of treatment modalities in clinical research (Joffe and Truog 2008). Clinical equipoise is a genuine disagreement among health care professionals about the best form of treatment for a particular disease or condition (Freedman 1987). Disagreement exists because the available evidence does not favor one treatment over another. The purpose of an RCT is to obtain evidence to help resolve disagreements concerning medical treatment (Miller 2008b). Clinical investigators may initiate on RCT, according to this view, only when equipoise exists (Miller and Weijer 2003). Randomly deciding a patient's treatment when equipoise does not exist is unethical because it violates the physician's duty to provide his or her patients with the best treatment (Miller and Weijer 2003). Placebo-controlled trials are ethical, according to this view, only if there is no effective treatment for the disease or

condition, because there would be a genuine disagreement about whether an experimental treatment is superior to a placebo (Miller and Weijer 2003; Chiong 2006; Joffe and Truog 2008). If an effective treatment exists, then an RCT should use an active-control study design, i.e. it should compare an effective treatment to an experimental one or evaluate different treatments that fall within the standard of care (see discussion of the HIV prevention trials in Chap. 1).

Miller and Brody (2002, 2003) have challenged the equipoise requirement by arguing that the ethics of clinical research is different from the ethics of clinical medicine, because the goal of clinical research is to develop generalizable knowledge, not to promote the best interests of patients (Litton and Miller 2005).[5] Patients may benefit from participating in clinical research, but studies are designed to develop medical knowledge, not necessarily to benefit individual patients (National Commission 1979). When patients consent to participate in clinical research, they are told how their treatment will differ from standard care, and that the goal of the study is to gain new knowledge.

Clinical research differs from clinical medicine in several ways. First, clinical investigators must provide treatment according to rules established by the protocol; they are not allowed to individualize treatment because doing so would compromise the quality of the data by introducing uncontrolled variables into the RCT. Second, clinical investigators and their staff often perform tests and procedures on patients for the sole purpose of collecting data or samples for research, not to benefit the patient (Miller and Brody 2002). In clinical medicine, the main reason for conducting a test or procedure on a patient is to obtain information that can be useful in diagnosis, prevention, or treatment. Third, clinical research includes procedures, such as randomization and double-blinding, which are not used in clinical medicine.

Others have challenged the notion that clinical equipoise is required before one may initiate an RCT on the grounds that physicians do not have an obligation to provide the best available treatment to their patients, if their patients have consented to receiving less than optimal therapy and they know their different options (Miller and Brody 2002). For example, the best treatment for a disease may be a new expensive medication that is still under patent. A patient may decide to take a medication that is less effective and expensive than the new medication because he or she cannot afford the new one. It would be acceptable for the physician to prescribe the less effective medication in this situation to accommodate the patient's financial needs, if the physician informs the patient about the option of taking the expensive medication. A cancer patient may decide to forego chemotherapy to have a good quality of life in his or her remaining days, even though chemotherapy would be the most effective treatment for his or her disease. Patients receiving care in teaching hospitals or medical centers may agree to allow students or trainees to perform procedures on them under the supervision of a health professional. Although the best care

[5] Some writers have challenged the equipoise requirement on the grounds that clinical equipoise is a poorly defined, vague concept. I will not explore that critique here. See Gifford (2000), Miller and Joffe (2011).

would be provided by someone who already has the appropriate training and experience, most of us would agree that it is ethical to allow students and trainees to practice on patients because helps them to learn, which is an important social goal (Chiong 2006). Thus, if a patient can consent to receiving suboptimal medical care in these situations, a patient may also consent to having his or her treatment randomized when equipoise does not exist, provided that the physician informs the patient of his or her options, including the option of not participating in research and obtaining treatment outside of a study, if it is available (Chiong 2006; Resnik 2009a).

The dispute concerning the equipoise requirement involves a conflict between promoting the welfare of patients/subjects and advancing scientific knowledge (Resnik 2009a). Proponents of the equipoise requirement argue that patients' best interests must take precedence over scientific objectives, while critics of the requirement argue that patients' best interests need not always take precedence if patients agree to place their well-being at risk for the sake of science.

The principle of trust implies that investigators should do their best to avoid betraying the trust of their patients when they enroll them in clinical studies. Since most patients expect that their treatment will not be chosen at random, investigators should ensure that patients/subjects understand that treatment will be randomly assigned if they are participating in an RCT. Patients should also understand that the study includes a placebo control group that they may receive a placebo instead of a treatment thought to be effective. The potential for therapeutic misconception looms large here, since patients/subjects often do not understand the difference between research and therapy and they may not understand that the treatment they receive will be chosen at random (Appelbaum and Lidz 2008). Investigators who enroll patients in RCTs have a duty to counteract the therapeutic misconception to ensure the validity of consent and avoid betraying their patients' trust (Miller and Brody 2002). As long as patients understand that their treatment will be chosen at random and they agree to this method of making treatment decisions, they can participate in RCTs when equipoise does not exist (Miller and Brody 2002).

7.10 Placebo-Controlled Trials

Many RCTs include placebo control groups to minimize bias due to the placebo effect (see discussions in Chaps. 1 and 5). In thinking about managing the risks of studies with placebo control groups it is useful to distinguish between three types of studies:

(A) Studies in which there is no effective treatment and subjects are randomly assigned to receive a placebo or an experimental treatment. Some of these studies may involve a crossover design in which patients receive a placebo during one phase and then receive an experimental treatment during another phase. These studies seek to compare the experimental treatment to a placebo.

(B) Studies in which there is an effective treatment and subjects are randomly assigned to receive a placebo, a standard treatment, or an experimental treatment. These studies, which may also include a crossover design, seek to compare the experimental treatment to a standard treatment and a placebo.
(C) Studies in which there is an effective treatment and subjects are randomly assigned to receive an effective treatment combined with placebo or an effective treatment combined with an experimental therapy. These studies, which also may include a crossover design, seek to compare different combinations of treatments, e.g. treatment A and experimental treatment vs. treatment A and placebo, etc.

Studies of type (A) and (C) do not generate as much ethical controversy as studies of type (B) because they do not require patients to forego an effective treatment. In studies of type (A), there is no effective treatment, and in studies of type (C) patients receive an effective treatment and a placebo. Asking patients to participate in studies of type (B) raises three types of ethical concerns. The first, which we discussed in the previous section, is that studies of type (B) violate the equipoise requirement. However, I argued earlier that equipoise is not necessary to initiate in RCT, since patients may consent to having their treatment randomized, even if this means that they may receive less than optimal treatment.

The second ethical concern is that it may be possible to achieve the study's aims by using an active-control rather than a placebo-control design. If the aims of a study can be achieved by using an active-control design, then one should use it, since this would allow all subjects to receive treatment for their disease (Lurie and Wolfe 1997; Miller and Weijer 2003). However, there are sometimes sound methodological reasons for using placebo-control designs when effective treatments are available. Some therapies, such as treatments for depression and pain, are only slightly more effective than placebos (Tempel and Ellenberg 2000; Emanuel and Miller 2001; Laughren 2001). If investigators have evidence that an established treatment is marginally more effective than a placebo, then to determine whether a new therapy is effective it may be necessary to include a placebo control group, since showing that the new therapy is as effective as the established therapy may not prove that it is clearly better than a placebo (Tempel and Ellenberg 2000; Laughren 2001).[6] The HIV RCTs discussed in Chap. 1 included placebo control groups to determine whether a short course of AZT would be more effective than a placebo at preventing mother-child transmission of the disease. If those studies had not

[6] For example, suppose that a hypothetical drug (Drug A) used to treat depression has been shown to be 35% effective as compared to a placebo (29%), with a standard error of 5%. Since the placebo lies outside the standard error, we can say that the drug is barely more effective than the placebo. Suppose that we compare a new drug (Drug B) to Drug A and find that Drug A is 35% effective and drug B is 34% effective, with the same standard error of 5%. Since Drug B is only 5% more effective than the placebo from the earlier trial, this active-control study does not tell us whether Drug B is more effective than a placebo, because its effectiveness is within the standard error. To find out whether B is more effective than a placebo, we would need to conduct a study that includes a placebo control group or initiate a much larger active-controlled study to reduce the standard error.

included placebo-controls, investigators would have had difficulty addressing this question (Varmus and Satcher 1997).

If we assume that there are good scientific reasons for conducting placebo-control RCTs, then we confront the third ethical concern: placebo-control studies may cause harm (Emanuel and Miller 2001; Miller 2008b). Harm may occur because patients need to stop taking medications used to treat their disease to participate in an RCT. Patients in placebo control groups could suffer serious harm from going off their medications. For example, a patient who stops taking a medication to control diabetes could develop dangerously high blood sugar or a patient who stops taking a medication for depression could become suicidal (Shamoo and Keay 1996; Bell 2001). Additionally, many clinical trials include a washout period before the study begins in which all patients stop taking medications related to the disease under investigation for a period of time. The purpose of the wash-out period is to control for the effects of these medications and avoid drug interactions. The length of the washout period depends on how long it takes for the body to eliminate the relevant drugs (DuVal 2004). Although all patients in these studies may experience harms related to the washout period, patients in the placebo groups may experience more harms because they will be foregoing medications during the washout period and throughout the study.

Harm could also occur because the placebo is not benign. Although placebos are usually innocuous substances ingested by mouth (e.g. sugar pills), some are far from harmless (Miller 2008b). For example, when a protocol requires patients to receive a medication intravenously through a catheter placed in a vein in the arm, investigators will catheterize all subjects, including those in the placebo group. Potential harms of catheterization include infection, bleeding, and discomfort (Schmid 2000). If an experimental medication has side-effects that patients are likely to know about, such as nausea, then the placebo may be designed to mimic those effects. Sham surgery represents an extreme case of placebo-related harm (Miller 2003). In a sham surgery study, patients receive a surgical intervention under investigation or a sham intervention, e.g. a surgical incision at the same location but not the complete surgical procedure. Patients who receive sham surgery may need to receive anesthesia and other interventions that are part of the surgery.

There are a number of strategies investigators can use to minimize harm to patients who receive placebos (Emanuel and Miller 2001). First, investigators should carefully monitor subjects during the study and the washout period. If a patient becomes seriously ill, the investigator may withdraw the patient from the study and provide him or her with appropriate treatment (Shamoo and Keay 1996). If the study is blinded, the investigator could un-blind it for that patient to determine whether he or she was receiving a placebo, a standard therapy, or an experimental treatment. Second, investigators can use DSMBs to monitor data and safety. If the data indicate that one group in a study is experiencing significantly more SAEs than another group, the DSMB may recommend that the study be stopped to protect patient/subjects from harm. The groups could be un-blinded to determine which treatment they were receiving. It may be the case that patients in the experimental group are faring worse than those in the placebo group (Friedman and Schron 2008).

Third, investigators should promptly report all SAEs and other problems to IRBs, DSMBs, and sponsors to allow them to make decisions needed to protect human subjects from harm.

In thinking about whether the risks of placebo-control studies are reasonable in relation to benefits, we need to consider the nature of the risks (Emanuel and Miller 2001). Miller (2008a, b) distinguishes between the probability, severity, and duration of the potential harm. At one end of the spectrum would be placebo-control studies in which potential harms are minor, short-term symptoms (such as headache, heartburn, nausea); at the other end would be studies in which potential harms are significant or long-term (such as diabetic crisis, stroke, paralysis, or death). Most people would agree that studies which have a high probability of causing significant or long-term harms to subjects receiving placebos would be unethical, but what about studies at the safer end of the spectrum? As mentioned in Chap. 1, the Helsinki Declaration states that the risks of receiving a placebo when there is an effective therapy must not be serious or irreversible (World Medical Association 2013). But this guidance is not very useful, because it does not say what it means for a risk to be "serious." The latest version of Council for the International Organizations of Medical Sciences (2016) guidelines recommends that risks should be only a minor increase over minimal risk. But what constitutes a "minor increase" over minimal risk?

Perhaps the concept of maximum risk, which I discussed above, can provide us with some useful guidance concerning acceptable risks. If we think of subjects in the placebo group as analogous to healthy volunteers because they are not receiving significant medical benefits from their participation (Miller 2008b), we can set a maximum risk for these subjects as: SAE risk not greater than 1% and mortality risk not greater than 65/100,000. Subjects could have a higher probability of experiencing symptoms and medical problems, such as headache, nausea, high blood pressure, fever, or mild depression, which do not rise to the level of an SAE. For example, a placebo-controlled study which asks mildly depressed subjects to forego medications would be acceptable under this approach, but one that asks moderately or severely depressed patients to forego medications would not be because it would involve a significant risk of suicide (Simon and Vonkorff 1998). Sham surgery involving general anesthesia would be ethically questionable under this standard. While the main risk of the surgery, anesthesia, has a mortality rate of 1/100,000, it has an SAE rate of 8% (see Table 7.1). Sham surgery involving only local or regional anesthesia would be more ethically acceptable under this standard, due lower risks of SAEs. (We will consider other issues related to placebo-control RCTs again in Chap. 8.)

7.11 Risks to Researchers and Third Parties

Some research studies pose risks to researchers and third parties (Resnik and Sharp 2006; Resnik 2012a, c, d). Examples include:

- Clinical trials that enroll pregnant women or lactating women may expose fetuses of infants to dangerous drugs (Grady and Denny 2008);

- Vaccination experiments which involve the administration of transmissible biological agents may create risks for researchers, family members or others who come into contact with the research subjects;
- Asthma studies involving pesticide treatments in the home to control insect allergens may create health hazards for occupants who come into contact with the chemicals (Resnik and Zeldin 2008);
- Thyroid cancer studies that require patients to ingest radioactive iodine may expose family members or others to hazardous radiation emitted by the patient (Wald 2010);
- Community-based research may yield information that could lead to stigma, bias, or discrimination against community members (Resnik 2012a);
- Administering chemotherapy to patients in oncology trials may exposure research staff to harmful chemicals;
- Xenotransplantation experiments could introduce zoonoses to research subjects which could spread to researchers, family members, and the human population (Melo et al. 2001)[7];
- Studies involving patients with communicable diseases could place researchers at risk for infection.

In this book, I have already addressed some issues involving third party risks, including risks to communities (see discussion of community issues in Chap. 5) and risks to family members (see discussion of confidentiality issues in Chap. 6). In this section, I will explore the ethical rationale for addressing risks to researchers and third parties.

Aside from the special protections for pregnant women and fetuses in Subpart B of the Common Rule and protections for pregnant and lactating women in the EPA's human research rules (see discussion in Chap. 2), the federal regulations do not address risks to third parties or researchers. The regulations focus on risks to human subjects (Resnik and Sharp 2006) and even discourage IRBs from considering some types of third party risks: "The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility (45 CFR 46.111a2)." The risks addressed in this passage have little to do with the risks mentioned above (e.g. risks to families, communities, etc.), since these are risks related to policy development.

While the federal research regulations do not require investigators or IRBs to address risks to researchers or third parties, one could argue that they nevertheless have an ethical obligation to deal with these risks, based on the principle of nonmaleficence (Resnik and Sharp 2006; Council for the International Organizations of Medical Sciences 2016). Investigators and IRBs have an ethical duty to minimize harms resulting from research, including harms to researchers and third parties. When deciding whether risks are reasonable in relation to benefits, IRBs should consider risks to researchers and third parties, not just risks to subjects (Resnik and

[7] Xenotransplantation is transplantation of tissues or organs across species, e.g. pig-human; a zoonosis is a disease transmitted from a vertebrate animal to a human.

Sharp 2006). Additionally, the principle of trust implies that investigators and IRBs should address some types of risks beyond those that that impact human subjects, since harms to family members, communities, or the public may erode trust. A pandemic triggered by a zoonosis transmitted to the human population from a xenotransplantation experiment would seriously damage the public's trust in the scientific enterprise, for example.

In many cases, investigators and staff can take steps to minimize risks to themselves or third parties (Resnik and Sharp 2006). For example, research staff who are working with human body fluids or tissues or dangerous chemicals can wear protective clothing prevent exposures to pathogens or toxic substances; investigators who are studying communities can consult with community representatives to address risks to the community; oncology researchers can instruct cancer patients who ingest radioactive iodine on how to avoid exposing other people to radiation; and investigators who are treating homes with pesticides can tell occupants to avoid contact with areas where residue may persist.

In some situations, however, it will be difficult to minimize risks, and IRBs must make decisions about whether or how these studies should be conducted (Resnik and Sharp 2006). For example, most drug studies routinely exclude pregnant women due to concerns about risks to the developing fetus and legal liability (Grady and Denny 2008). However, some studies that pose risks to fetuses may offer significant medical benefits to pregnant participants and women's health (Lyerly et al. 2008, 2011). For example, pregnant women may benefit from participating in studies of antidepressant medications or drugs used to treat tuberculosis (Lyerly et al. 2011; Gupta et al. 2016). IRBs must decide whether to exclude pregnant women from studies that could benefit them. (Issues related to including women in research will be discussed in more depth in Chap. 9.) As noted above, xenotransplantation studies may pose significant public health risks related to the transmission of zoonoses to people who come into contact with the recipient. While the probability of widespread contamination may be low, this risk could be serious, given the scope of potential harm and the possibility that human beings may have no natural immunity to the pathogen (Melo et al. 2001). IRBs must decide whether the risks of these studies are reasonable in relation to expected benefits.

7.12 Compensation for Research-Related Injuries

As we have seen in this book, human subjects are sometimes injured as a result of participating in research. Injuries range from relatively minor problems, such as infections, benign allergic reactions, or short-term toxicity, to catastrophic events, such as stroke, cardiac arrest, or permanent disability or death (Steinbrook 2006; Resnik et al. 2014). The federal research regulations do not require investigators, institutions, or sponsors to compensate human subjects who are injured in research, although they do require investigators to inform subjects who are participating in more than minimal risk research about "whether any compensation and an

explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained (45 CFR 46.116a6)." The federal regulations also prohibit informed consent documents or discussions from including "any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence (45 CFR 46.116)."

Resnik et al. (2014) conducted a survey in 2012 of the compensation for injury policies of the top 169 U.S. academic institutions ranked by total research funding and compared data they obtained to data collected in 2000 of 127 institutions from a study conducted by Parasidis (2001). The survey by Resnik et al. (2014) found that 51.2% of institutions offered no compensation in 2012, compared to 56.1% in 2000; 36.9% offered compensation if certain conditions are met, compared to 31.8% in 2000; 8.1% offered compensation at the discretion of the institution or sponsor, compared to 11.2% in 2000, and 3.8% offered compensation without any conditions, compared to 0.9% in 2000. The only statistically significant difference between data from 2012 and 2000 emerged when the analysis focused on institutions included in both studies. Of these 57 institutions, 9.1% changed from no compensation in 2000 to discretionary compensation in 2012 ($p < 0.001$) (Resnik et al. 2014). The authors noted that some institutions may provide medical treatment or some other form of compensation to injured research subjects even though they do not have an official policy that requires them to do so (Resnik et al. 2014).

Since the 1970s, numerous government commissions and commentators have recommended that the U.S. require that institutions or sponsors compensate human subjects for research-related injuries (National Bioethics Advisory Commission 2001a; Pike 2012). However, the study by Resnik et al. (2014) indicates that substantial changes to compensation for injury policies will probably not occur without a U.S. government mandate (Resnik et al. 2014). Although the U.S. federal government does not mandate that research subjects receive compensation for injuries, many European, Asian, and African governments do (Pike 2012).

If an institution or sponsor refuses to compensate a research subject for his or her injuries, the subject's only recourse in the U.S. is to sue for damages. However, relying on the legal system to rectify harms is neither an effective nor a fair method of compensation since injured research subjects may have difficulty prevailing in court or obtaining a satisfactory settlement, and some may be barred from obtaining compensation, due to legal defenses, such as government immunity or assumption of risk. Moreover, it may take many years for injured research subjects who win their cases to receive compensation (Pike 2014).

It is worth noting that some institutions have exemplary compensation for injury policies. The NIH's Clinical Center, the Department of Defense, and the Department of Veterans Affairs provide injured research subjects with free access to short-term medical care (Pike 2012). Since 1979, the University of Washington has a self-funded compensation plan that provides injured research subjects with up to $250,000 in medical treatment (Pike 2012). Medicare also covers the cost of treatment for research subjects injured in qualifying clinical trials (Pike 2012).

There are several ethical arguments for providing injured research subjects with some form of compensation (Resnik 2006; Pike 2012). First, compensatory justice requires that investigators, institutions, or sponsors compensate human subjects for their injuries, since responsible parties should rectify the damages that they have caused. Second, distributive justice requires that research subjects receive compensation for their injuries, since people who are harmed in research may bear an unfair burden of the financial and non-financial costs of research. To ensure that the costs are distributed more fairly, injured subjects should receive some form of compensation, i.e. money, medical treatment, or both. Third, compensating injured research subjects can help prevent additional harms that may occur if they do not receive treatment because they lack health insurance and cannot afford to pay for their own care (Pike 2012; Resnik et al. 2014). For example, if a subject does not receive treatment for an infection related to the placement of catheter in his arm, his infection could spread and threaten his health or life. Finally, the principle of trust also implies that institutions or sponsors should compensate human subjects for their injuries, since failing to provide subjects with medical treatment or some of other form of compensation when they are injured would undermine their trust in institutions and sponsors and would add insult to injury (so to speak).

Scott (2003), Resnik (2006) and Pike (2012) have proposed no-fault compensation systems for research injuries. Resnik's proposal, which is modelled after the U.S. National Vaccine Injury Compensation Program, includes four elements. First, subjects should be eligible to receive compensation regardless of whether they are partly responsible for their injuries. Second, panels composed of doctors, scientists, and other experts would review compensation claims filed by research subjects to determine whether they have been injured and what form compensation should take. Third, immediate medical care would be provided to subjects who require it. Fourth, institutions and sponsors would contribute money to a national insurance pool to cover the costs of compensation, including short-term and long-term medical care, if necessary (Resnik 2006).

The main argument against compensating injured research subjects is economic: sponsors and institutions might object that compensation programs are too expensive. While compensation programs are likely to increase the costs of conducting research, they may also save money by helping sponsors and institutions reduce litigation expenses (Resnik 2006). Another objection to compensation programs is that they may be cumbersome implement, but this problem can be overcome through careful planning and ample funding for administrative costs.

7.13 Conclusion

The topic of risk takes center stage in many ethical issues in research involving human subjects. Although I have discussed issues related to risk in the previous chapters of this book, and will revisit risk issues again in subsequent ones, in this chapter I have focused on questions related to risk. I have considered general

questions concerning risk, such as defining minimal risk, and minimizing and managing risks, as well risks related to specific types of research, such as studies involving healthy volunteers or placebo control groups. I have considered how the principles of respect for dignity/autonomy, non-maleficence, beneficence, justice, and trust apply to questions concerning research risks. In the next chapter I will focus on the other side of the risk/benefit coin, i.e. benefits to subjects and society.

Chapter 8
Benefits

In the previous chapter, I applied the trust-based approach to ethical issues related risks to research with human subjects. In this chapter, I will shift the focus from risks to benefits. As noted in the last chapter, the federal regulations require that risks be reasonable in relation to the benefits to the subjects or the importance of the knowledge expected to be gained (45 CFR 46.111). Other guidance documents, such as the Nuremberg Code (1949), Belmont Report (National Commission 1979), Helsinki Declaration (World Medical Association 2013), and Council for the International Organizations of Medical Sciences guidelines (2002, 2016) include similar statements concerning research benefits. Although few people would dispute the notion that research with human subjects should yield benefits for subjects or society, ethical issues can arise concerning the interpretation and application of the principle of beneficence in research. Before examining these examining issues, it will be useful to define the term 'benefit.'

8.1 What Are Benefits?

A benefit is something we regard as valuable or good, such health, food, clothing, shelter, self-esteem, happiness, virtue, knowledge, wealth, money, or freedom. We may value a benefit for its own sake (i.e. intrinsically), for what it can do for us (i.e. extrinsically), or for both reasons. For example, most of us would regard happiness as intrinsically valuable, but would view money as only extrinsically valuable because we value money for what we can do with it. Many of us would value health for its own sake and for what it can do for us, because we need good health to work or engage in physical activities. Benefits may accrue to individuals, communities, or society. Public health, economic development, national security, and clean air are examples of social benefits (Resnik 2016a).

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8.2 What Are the Benefits of Research?

Research with human subjects offers many potential benefits to individuals, communities, and society. Research can benefit individuals by providing them with access to medical care or information about their health which may be useful in diagnosis, treatment, or prevention. Individuals who participate in research may also derive a sense of satisfaction or self-esteem from contributing to a project they view as worthwhile. Although federal guidance discourages IRBs from treating money as a benefit, most people appreciate receiving payment for their participation (Njue et al. 2014).[1] Research can benefit communities by providing access to treatments or public health interventions, or by contributing to local health care infrastructure, education, or economic development (Pratt and Loff 2014). Research can benefit society by promoting the growth of human knowledge, which may contribute to the development of medical treatments, public health practices and interventions, and may enhance our understanding of human biology, psychology, culture, and social interactions. Research may also help to inform public policies (Resnik 2009b).

8.3 What Is the Relationship Between Research Design and Benefits?

Sound research design is widely recognized as a key principle of research ethics, since poorly designed studies may not generate data or results that benefit society (Emanuel et al. 2000). Although the federal research regulations do not address research design per se, they imply that studies should be well-designed, since the risks of research cannot be reasonable if a study is not likely to yield important benefits (Emanuel et al. 2000).[2] The Nuremberg Code (1949), Helsinki Declaration (World Medical Association 2013), and Council for the International Organizations of Medical Sciences (2016) guidelines also address the importance of good research design. Although IRBs are supposed to focus on ethical/legal issues, they can also address research design issues as far as these impact risks and benefits. IRBs often include members with expertise in the relevant scientific areas who are qualified to comment on study design issues. IRBs may also consult with outside experts on scientific or ethical issues. Ideally, studies should undergo some form of scientific review prior to IRB review to ensure that research design issues are adequately addressed and allow the IRB to focus on ethical/legal issues (Resnik 2015d).

[1] The rationale for this position is that treating money as a benefit might allow IRBs to approve very risky studies that offer healthy volunteers money as a benefit. However, I would argue that IRBs can avoid doing this by establishing a level of maximum risk for healthy volunteers in research. See discussion in Chap. 7. Thus, it is possible to treat money as a benefit and protect human subjects from excessive research risks (Wertheimer 2011).

[2] The criteria for rigorous study design are beyond the scope of this book and far too numerous to explore in-depth here. See Gallin and Ognibene (2012).

8.4 Sources of Special Duties of Beneficence

As noted in Chap. 3, numerous ethical theories support general duties of beneficence to all human beings, including strangers. We also noted, however, that general duties to benefit others are not absolute and must be balanced against competing moral considerations, such as personal needs and interests, and other obligations, and so on. Special duties of beneficence are obligations to help others we acquire as a result of our relationships or activities. These special duties are stronger than general duties of beneficence and often take priority over other obligations or interests. For example, one might argue that a mother's duty to feed her child outweighs her obligation to feed a stranger or her desire to buy a new dress. Some of these special duties include: family-related (e.g. parent-child, child-parent), friendship-related, partnership-related, trustee-related, and professional related (e.g. doctor-patient, lawyer-client). In addition, one might argue that we can acquire special duties of beneficence based on our unique resources or abilities. For example, if you are the only one nearby who is trained in cardiopulmonary resuscitation (CPR) and someone has a heart attack in your proximity, you have a special obligation to provide CPR to that person, given your training. In this chapter, we will consider whether investigators sometimes have special duties of beneficence based on their relationships to research subjects or their resources or abilities (Richardson and Belsky 2004).

8.5 Disclosing Individual Research Results to Human Subjects

Investigators frequently collect data that may be useful to research subjects, such as information obtained from physical examinations (e.g. blood pressure, heart rate, swollen lymph nodes), laboratory tests (e.g. blood sugar levels, environmental exposures, genetic/genomic variants), interviews (e.g. depression screening), and imaging studies (e.g. abnormal findings detected by X-rays, ultrasounds, or MRIs) (Wolf et al. 2008; Beskow and Burke 2010; Jarvik et al. 2014). The information that investigators disclose to research subjects may be useful for making medical or reproductive decisions, or managing hazards in the home or workplace. For example, in the KKI study (discussed in Chap. 2) the investigators collected information on children's exposures to lead in the home. Parents of two children in the study sued the investigators and KKI on the grounds that they failed to disclose lead exposure information in a timely fashion (Grimes v. Kennedy Krieger Institute, Inc. 2001). The parents could have used that information to protect their children from lead-related hazards.

Bioethicists and investigators began paying closer attention to ethical issues related to the return of research results about 15 years ago, and there is now an extensive literature on the topic. Federal research regulations do not require investi-

gators to share research results with human subjects unless the information may affect their willingness to continue participating in the study (45 CFR 46.116b5). The Presidential Commission for the Study of Bioethical Issues (2013) has made some distinctions which are useful for thinking about the issues at stake:

Individual vs. Aggregate Results Individual results pertain to particular research subjects (e.g. a child's lead exposure); aggregate results pertain to the whole population under investigation (e.g. the results of on breast cancer genomics).

Primary vs. Secondary Results Primary results are results investigators seek to collect in order to achieve the aims of study; secondary results are other results collected as part of a study. For example, pulmonary function tests results might be the primary results of an asthma study while liver function test results might be secondary results.

Incidental vs. Targeted Findings Incidental findings are results that are discovered while conducting research but not primary or secondary results. For example, an investigator who is studying fibroid tumors in women might discover an abnormal growth when conducting ultrasound examination of a woman's uterus. An abnormal growth would be an incidental finding, whereas a fibroid tumor would be a targeted finding.

There has been little ethical debate about sharing aggregate results with human subjects. Most commentators agree that it is appropriate for investigators to share these results with participants, since they may want to know how the study turned out. Most of the ethical debate has focused on the obligation to disclose individual results, including incidental findings (Wolf et al. 2008).

There are two main arguments for disclosing individual results to research participants. The first is that disclosure can benefit research participants (Fernandez et al. 2003; Wolf et al. 2008; Beskow and Burke 2010). For example, an investigator who discovers that a subject has abnormally high blood pressure can share this information with the participant to help him or her avoid additional health problems. If the subject's blood pressure is dangerously high, the investigator could provide emergency treatment or call an ambulance. If the subject's blood pressure is moderately high, the investigator could recommend that the participant see a physician and could provide a referral, if necessary. One might argue that investigators have special duties to benefit research subjects, given the nature of their relationship and their unique resources or abilities (Richardson and Belsky 2004).

The second argument is that disclosure can empower subjects to make autonomous choices (Fernandez et al. 2003; Shalowitz and Miller 2005). For example, a research subject who learns that she has a genetic mutation that triples her lifetime risk of developing breast cancer can use this information to make decisions concerning lifestyle changes that she can implement to reduce her risk of developing the disease. She may also decide to undergo more frequent breast examinations to detect tumors early or to inform female family members about her mutation, in case they want to be tested. Providing subjects with targeted or incidental research findings can enhance their autonomous decision-making.

Studies indicate that most research subjects want to receive individual results (Shalowitz and Miller 2008). For example, Fong et al. (2004) found that 90% of 429 survey respondents would want to individual results from research on stored biological samples and 80% would want these sent to their physicians. Hoeyer et al. (2004) found that 55% of 600 survey respondents would want to receive tests results concerning genetic predispositions for disease if treatment is available. Brody et al. (2007) found that 97% of 120 participants in a household environmental exposure study wanted to receive individual and aggregate results. Bollinger et al. (2012) found that most participants in 10 focus groups wanted to receive individual results from genetic research.

It makes little ethical difference whether individual research results that investigators share with subjects are targeted or incidental, since participants can benefit from—and may want to receive—both types of results. For example, a patient could benefit from learning that he has high blood sugar, regardless of whether his blood sugar level was a targeted or incidental finding. The main difference between targeted and incidental findings is logistical: investigators may be well-prepared to deal with targeted findings, since they are looking for them, and they may not be well-prepared to deal with incidental findings, since they are not actively looking for them. Since it is important for investigators to respond to incidental findings that may be useful to research subjects, they should plan accordingly (Presidential Commission for the Study of Bioethical Issues 2013).

While beneficence and autonomy favor disclosure of individual research results, other ethical considerations may caution against it. First, disclosure may do more harm than good in some cases. For example, a false positive test result could cause a research subject needless stress and anxiety, whereas a false negative result might lull a subject into an erroneous sense of security (Wolf et al. 2008; Resnik 2011a, b). To minimize the possibility of returning invalid test results, investigators should follow procedures that promote data quality and integrity. Investigators should ensure that staff members are well-qualified to perform tests and examinations, and they should send biological samples to laboratories which follow procedures designed to enhance testing accuracy and precision. Ideally, the laboratories should have CLIA (Clinical Laboratory Improvement Amendments) certification (Ravitsky and Wilfond 2006). If a research subject has a positive result for a clinically significant outcome (such as HIV antibodies, high white blood cell count, etc.), he or she should be retested to ensure that the result is accurate.

Harm may also occur when the results are valid but have uncertain clinical or practical implications (Jarvik et al. 2014). For example, suppose that investigators discover that a participant has several genomic variants which together increase the risk of developing Alzheimer's dementia at age 70 by 10%. Suppose there is also no effective method of preventing or treating this disease. Sharing these genomic findings with this research subject might cause him considerable worry without offering him substantial benefits (Renegar et al. 2006). Moreover, he might misunderstand the implications of the findings and take drastic measures to deal with them, such as deciding to commit suicide before reaching the age of 70. Or suppose that investigators who are conducting research on in-home exposures to industrial chemicals dis-

cover that a family has an abnormally high exposure to a type of flame retardant. However, studies on the health implications of exposure to the flame retardant have been inconclusive. The family might suffer from needless anxiety if they receive this result and they might make an ill-advised choice to sell their home. In some cases, subjects might undergo expensive and painful medical tests as a result of receiving uncertain results. For example, a man who learns that he has an elevated prostate specific antigen level might decide to have a prostate biopsy. Ethicists and researchers who are concerned about the harmful effects of disclosing research results argue that investigators should only disclose results which have a definite clinical or practical value (Wolf et al. 2008; Beskow and Burke 2010; Resnik 2011a, b; Presidential Commission for the Study of Bioethical Issues 2013).

There has been little research on the impacts of sharing uncertain tests results with research subjects, so these supposed harms are largely speculative at this point. A couple of studies have found that some women have a difficult time dealing with inconclusive results from genetic tests for breast cancer risk and that their reaction depends on their tolerance for uncertainty (O'Neill et al. 2006; van Dijk et al. 2006). Other studies have found that most adverse psychological reactions to inconclusive genetic test results dissipate over time (Hamilton et al. 2009). Brody et al. (2007) found that participants in their study of in-home chemical exposures had little difficulty dealing with uncertain tests results. Clearly, more research is needed on this topic. Until we have a better understanding of the impact of informing research subjects about uncertain individual research results, precaution may be the best policy (Resnik 2011a, b).

An argument against mandated disclosure of individual tests results is that some research subjects may not want to receive some or all of their individual research results. Subjects may not want to receive results that have uncertain clinical or practical value so they can avoid needless worry or stress. Many commentators have argued that investigators should respect subjects' preferences concerning disclosure of results and that they should not share findings with them that they have elected not to receive (Shalowitz and Miller 2005; Resnik 2011a, b).

Cost is another factor to consider when deciding whether to share individual research results with human subjects, since disclosing individual results might interfere with the aims of the research by drawing financial resources away from other study activities (Resnik 2011a, b). Investigators who are conducting brain imaging studies on healthy volunteers, for example, may need to hire radiologists to examine images for incidental findings, such as possible tumors. Investigators who are conducting genetic or genomic research may need to hire genetic counselors to discuss results with participants (Jarvik et al. 2014). Investigators may also need to spend considerable time and effort locating research subjects to inform them of individual results, especially if they have moved and not provided the research team with their new contact information. Actively searching for incidental findings may also inflate the costs of research (Presidential Commission for the Study of Bioethical Issues 2013). One might argue that disclosure is not necessary

when the costs are significant and the benefits to the subjects are marginal (Affleck 2009). However, if the benefits of disclosure are high and the costs are low, then cost should not be a factor (Resnik 2011a, b). For example, it costs very little to inform a subject that he has dangerously high blood pressure and sharing this information with him could save his life.

Some commentators have pointed out that disclosing individual research results may contribute to the therapeutic misconception (see discussion in Chap. 5) by causing subjects to think that the purpose of the research is to provide them with medical benefits (Clayton and Ross 2006; Ravitsky and Wilfond 2006). Others have argued, however, that disclosure of individual results is not likely to contribute significantly to the therapeutic misconception, provided that investigators carefully explain the purposes of research to participants (Shalowitz and Miller 2008).

If we think about these issues from the perspective of promoting trust, we can see that it is important for investigators to disclose results which have clinical and practical value. Failing to share these results with research subjects in a timely fashion could undermine trust. For example, parents who sued the investigators and KKI probably felt a deep sense of betrayal when they learned that investigators had known for several months that their children had dangerous lead exposures but had not informed them. The parents' distrust of the investigators and KKI probably also had a negative impact on the community's perception of the institute. On the other side of the ledger, sharing results with clinical and practical value in a timely fashion can promote trust, since subjects are likely to feel that investigators care about them and want to promote their well-being. For example, a subject who learns for the first time that she has high blood sugar may be grateful to the research team for sharing this information with her and helping her get treatment.

Sharing research results with uncertain clinical or practical implications could positively or negatively impact trust. Disclosing these results could positively impact trust if subjects want to receive this information and the investigators help them understand its implications. For example, Brody et al. (2007) gave the subjects in their study information about their in-home chemical exposures, including a chart that compared their exposure levels to exposure levels for the average home. They also informed subjects about any dangerous exposures and steps they could take to reduce their exposures. Sharing uncertain results could negatively impact trust if subjects do not want to receive them, or they want to receive them but the investigators do not provide them with adequate counseling or advice. Subjects who receive their individual research results but get little counseling from investigators may feel overwhelmed or abandoned. Of course, subjects may feel overwhelmed or abandoned if they do not receive adequate counseling or advice related to research results with definite clinical or practical implications, but this problem is more likely to occur when they receive results which have uncertain clinical or practical value.

Four distinct positions have emerged in the debate about the return of individual research results (Brody et al. 2007). The first is that investigators are not obligated to return individual results, since the data and samples are collected for the purpose of research, not to provide subjects with medically useful information. This position may be defensible for some types of research. For example, it would not be feasible

for investigators who are collecting anonymous biological samples for research to share individual results with subjects, since the samples would need to re-identified, which might be impossible or prohibitively expensive. However, one could argue that when investigators are collecting identified samples and data and obtain medically useful information that they should share individual results with subjects. For example, investigators who are testing women for BRCA1 and BRCA2 mutations would be obligated to share these test results with the subjects, since it is well-established that BRCA1 and BRCA2 mutations increase the risks of breast cancer (Renegar et al. 2006).

The second position is that researchers should only disclose individual results which are reliable and accurate and have definite clinical or practical value (National Bioethics Advisory Commission 1999; National Heart, Lung, and Blood Institute Working Group 2010). This approach gives ethical priority to beneficence and non-maleficence (Resnik 2011a, b). The main drawback with this position is that it does not allow subjects to obtain results without a definite clinical or practical value which they nevertheless might be interested in receiving.

The third position is that investigators should disclose all individual results that subjects have chosen to receive (Fernandez et al. 2003; Brody et al. 2007). This approach gives priority to respect for autonomy and beneficence (Resnik 2011a, b). The main drawback with this position is that it may cause some subjects significant distress if they receive results suggesting possible health risks and they do not know how to respond to this information.

The fourth position, which I favor, is that one should make the disclosure decision on a case-by-case basis, taking into consideration the context of research (Ravitsky and Wilfond 2006; Beskow and Burke 2010; Resnik 2011a, b). In some cases, it will be appropriate to not disclose individual results; in other cases it will be appropriate to disclose some or all individual results. The advantage of this position is that it seeks to balance competing ethical principles, i.e. respect for dignity/autonomy, non-maleficence, and beneficence, while also promoting trust. Some contextual factors to consider when deciding whether full disclosure is appropriate include:

The Study's Design, Methods, and Goals As mentioned above, there may be some studies, such as research on anonymous samples or data, where it is not feasible to share individual results with human subjects.

The Clinical or Practical Value of Individual Results As mentioned above, some studies may generate results that have definite clinical or practical value for participants. Sharing individual results may be appropriate in these studies, provided that the results are reliable and the subjects receive appropriate counseling or advice.

The Subjects' Ability to Deal with Uncertain Results It may be appropriate to disclose all results to subjects who are well-educated, competent, actively engaged in the research process, and interested in knowing all of their results (Resnik 2011a, b). For example, Brody et al. (2007) recruited subjects who were concerned about their exposures to household chemicals and wanted more information. The subjects

were comfortable with receiving information about household exposures with indeterminate practical implications. Full disclosure may be less appropriate when most of the members of the population are likely to be poorly-educated, mentally impaired, disengaged from the research process, and not interested in knowing their all of their results.

The Depth of the Relationship Between Subjects and Investigators Full disclosure may be an appropriate option when investigators have long-standing relationships with research subjects marked by a high degree of trust, since the investigators are likely to have the personal rapport needed to discuss uncertain results with subjects. For example, full disclosure may be an appropriate policy when the subjects are cancer patients receiving treatment at a local clinic or hospital, but it may be less appropriate when the subjects are contributing blood samples to a biobank and have minimal contact with members of the research team.

The Costs of Disclosure Disclosing individual results may be appropriate when it will not significantly add to the costs of the study, but less appropriate when it will significantly add to the costs of the study.

Before concluding this section, it is important to say a few words about consent. Investigators should inform research subjects about any plans they have for returning aggregate or individual results to them, because informing them respects autonomy and promotes trust (Presidential Commission for the Study of Bioethical Issues 2013). Investigators should inform subjects about the types of results they may receive (e.g. results of laboratory tests or imaging studies, incidental findings, etc.), how they will receive them (e.g. in person, by phone, email, etc.), and when they will receive them (e.g. immediately, within a week, a month, etc.). They should also inform subjects about the availability of counseling, treatment, referrals, or other resources to help them understand and deal with their results, as well as the potential implications of tests results for family members (e.g. genetic testing).[3] Finally, investigators should give subjects the opportunity to decide not to receive some or all of their results.[4]

8.6 Ancillary Care

Ancillary care is another type of benefit that investigators might offer to research subjects. We already discussed this topic in Chap. 4 when examining Richardson and Belsky's partial entrustment view, but we will say a bit more about it here. At

[3] For example, if a woman tests positive for BRCA1/BRCA2 breast cancer mutations, she may want to inform her female relatives in case they want to be tested.

[4] This option may be limited in some situations. For example, in the U.S. health care professionals are legally obligated to report the results of HIV tests to patients and public health agencies. Patients cannot refuse to receive their HIV test results. They only way to not receive HIV test results is to opt-out of HIV testing.

least three moral principles support a duty to provide ancillary care to research subjects in some circumstances. First, the principle of beneficence implies that investigators, institutions, and sponsors have an obligation to provide ancillary care to research participants, because ancillary care can benefit them. One might argue that investigators have special duties of beneficence based on their relationships with research subjects and their resources and abilities (Richardson and Belsky 2004). Second, the principle of justice implies a duty to provide ancillary care to socioeconomically disadvantaged populations which may not have access to care outside of the study, as is often the case in research conducted in developing nations (Participants in the 2006 Georgetown University Workshop on Ancillary-Care Obligations of Medical Researchers Working in Developing Countries 2008; Dickert and Wendler 2009; Pratt et al. 2013). Providing ancillary care to disadvantaged research subjects can improve their health and therefore help to address socioeconomic inequalities. Third, the principle of trust implies that investigators, institutions, and sponsors should provide ancillary care because providing ancillary care can promote trust.

There are several arguments against providing ancillary care, however. First (as noted in Chap. 4), providing ancillary care may significantly increase the costs of research (Richardson and Belsky 2004; Dickert and Wendler 2009). If a sponsor is unwilling to provide additional funding to cover the costs of ancillary care, an investigator may need to shift money away from other study activities in order to provide ancillary care, which could interfere with his or her ability to achieve the aims the study and might violate the agreement with the sponsor concerning the management of research funds. Investigators may face a conflict between benefitting individual research subjects by providing them with ancillary care and benefitting the local population or the larger society by conducting a study that is adequately funded to achieve its goals.

Second, one might argue that providing ancillary care confuses the goals of research with the goals of human development. Although helping people who have significant medical needs is a worthy goal (London 2005), one might argue that the best way that investigators, institutions, and sponsors can help socioeconomically disadvantaged people is by conducting research that may benefit them. Other stakeholders, such as local governments, health agencies, or international relief/development organizations, should be responsible for providing health care to socioeconomically disadvantaged people and addressing issues of global justice (Participants in 2006 the Georgetown University Workshop on Ancillary-Care Obligations of Medical Researchers Working in Developing Countries 2008).

Third, (as also noted in Chap. 4), providing ancillary care may bias data and results in some cases, especially in observational studies which are collecting information on the health of a cohort (Hyder and Merritt 2009). For example, suppose that researchers are studying the health impacts of coal miners' exposure to occupational hazards. Treating the miners for diseases related to their work may bias the study results by giving the miners access to health care which they would not have had if they were not in the study.

Fourth, providing ancillary care may contribute to the therapeutic misconception (see discussion in Chap. 5) by encouraging human subjects to think that the main purpose of a study is to provide them with medical treatment, not to gain new knowledge (Resnik 2009a). Some research subjects may enroll in a study in order to receive ancillary care benefits.

While there are some compelling arguments for providing ancillary care in some situations, there are also sound arguments for not providing it. Looking beyond the general issue of whether to provide ancillary care, there are specific questions about who is responsible for providing or funding care and how much care should be provided (Participants in the 2006 Georgetown University Workshop on Ancillary-Care Obligations of Medical Researchers Working in Developing Countries 2008; Hyder and Merritt 2009). One could argue that investigators and research staff (such as nurses) are responsible for providing care in some situations, given their special duties of beneficence (discussed above). However, investigators and staff members may not be able to exercise their responsibilities if sponsors or are not willing to pay for ancillary care. Sponsors could argue that they are not responsible for funding ancillary care, since it is not part of the study. Sponsors might decide not to conduct research in areas where they may incur financially burdensome ancillary care responsibilities (Wertheimer 2011). In order to encourage sponsors to fund research that may include ancillary care, investigators, sponsors, institutions, and IRBs should clearly delineate ancillary care responsibilities prior to the initiation of the study. They should develop agreements concerning the types of care that will or will not be provided to research subjects. They may also need to collaborate with other stakeholders concerning the provision of medical care for research participants. Sponsors might agree to fund some types of care but ask other stakeholders to fund other types of care.

Given the ethical, logistical, and financial complexities of providing ancillary care in research, the most reasonable approach to the issues is to make ancillary care decisions on a case-by-case basis, taking the following factors in account (Richardson and Belsky 2004; Dickert and Wendler 2009):

The Health Care Needs of the Population What types of diseases or medical conditions are members of the study population likely to have? What types of treatment would be required? Can any of these diseases/conditions be treated relatively easily through a one-time intervention? Are some of these chronic illnesses which require ongoing treatment?

The Expectations of the Population Do members of research population expect to receive ancillary care? How will providing or not providing ancillary care impact trust?

Available Health Care Resources What types of health care resource are available to the study population? Are there local hospitals, clinics, or health departments which can provide medical care? Are international relief/development organizations active in the area?

The Costs of Ancillary Care How much would it cost to provide specific types of ancillary care? Can these costs be accommodated within the research budget? Is the sponsor willing to cover these costs?

The Goals of the Study and Research Methodology Will providing ancillary care interfere with achieving the goals of the study? Will it bias the data or results?

The Expertise and Skill of the Investigators and Research Team Investigators and research staff should have the expertise and skill to provide ancillary care. For example, it would irresponsible to ask a social scientist with no medical training to provide research subjects with treatment for infectious diseases.

The Depth of the Relationship Between Subjects and Investigators Will the investigators be interacting with the research subjects on multiple occasions? Providing ancillary care may make the most sense when investigators have long-standing relationships with research subjects marked by a high degree of trust (e.g. the investigators are conducting Phase II clinical trial), but it may make less sense if they have a temporary relationship (e.g. the investigators are collecting blood samples for a biobank).

8.7 Post-trial Access to Medications

The issue of post-trial access to medications emerged as hot topic during the 1990s, when investigators were conducting HIV/AIDS prevention or treatment clinical trials in resource-poor settings, such as developing nations.[5] Patients who had access to drugs used to combat HIV could not obtain these medications when studies ended, due to limited local health care resources. Many commentators argued that it was unfair and cruel for investigators and sponsors to provide patients with treatment during the trial and then abandon them once the trial ended. An international consensus emerged that investigators and sponsors have an ethical obligation to help secure post-trial access for treatment in resource-poor settings. The Helsinki Declaration includes a definitive statement concerning post-trial access obligations:

> In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process (World Medical Association 2013).

The 2002 CIOMS guidelines also address post-trial access, but with leave much more room for interpretation than the Helsinki Declaration:

[5] The terminology related to development has evolved over the years. Several decades ago, developing nations were referred to as "third world" nations. More recently, the term "low and middle-income countries" has come into fashion.

> Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that: the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community (Council for the International Organizations of Medical Sciences 2002:51).

The 2002 version of CIOMS guidelines covers post-trial access concern under the concept of "reasonable availability," which could mean many different things, including providing free treatments for study participants or members of the community, or ensuring that treatments will be marketed in the host community and sold at an affordable price. The 2016 version does not include the concept of reasonable availability but states that sponsors and researchers must:

> [M]ake every effort, in cooperation with government and other relevant stakeholders, to make available as soon as possible any intervention or product developed, and knowledge generated, for the population or community in which the research is carried out, and to assist in building local research capacity (Council for the International Organizations of Medical Sciences 2016:16).

Despite the existence of a broad consensus concerning the general idea that patients in clinical trials conducted in resource-poor settings should have post-trial access to treatments, many questions remain unsettled, such as: what is the justification for providing post-trial treatment? What is the scope of and extent of post-trial treatment obligations? Who is responsible for providing and funding post-trial treatment? Should sponsors be required to pay for post-trial treatment when it is not otherwise available? (Zong 2008; Millum 2011). The general agreement on the issue appears to stem from a common emotional reaction to a compelling human needs rather than a careful reflection on the ethical issues (Sachs 2011). Not surprisingly, most clinical trial participants in resource-poor settings believe that they deserve access to medications when the study ends (Pace et al. 2006).

Sofaer and Strech (2011) have conducted a systematic review of the bioethics literature on post-trial obligations and identified 36 types of reasons for or against providing access to these treatments. I will review a condensed list of arguments here, focusing on the sponsor's obligation to pay for post-trial antiretroviral treatment (ART) in HIV/AIDS research, since this issue has generated the most debate.

According to the beneficence argument, sponsors should pay for post-trial access to ART for research subjects to benefit them. Although we normally think of individuals as having moral duties, one might argue that organizations and institutions (such as private companies or government agencies) also have moral obligations, since they engage in activities that affect individuals, society, and the environment (Resnik 2011a, b). Hence, one could argue that research sponsors have duties of beneficence which imply an obligation to fund post-trial ART. A potential objection to this argument is that beneficence is not an absolute moral duty and must be balanced against other considerations, such as financial and resource constraints. I will

return to this point below when I consider arguments against post-trial treatment obligations.

According to the non-maleficence argument, sponsors should pay for post-trial ART for research subjects to avoid harming them when they lose access to those medications (Sofaer and Strech 2011). To evaluate this argument, we need to distinguish between two types of alleged harm:

Case 1: A has HIV prior to enrolling in a clinical trial testing an ART drug. A's health improves during the trial but then worsens when it ends because she no longer has access to ART.

Case 2: B does not have HIV prior to enrolling in clinical trial of an HIV vaccine. B develops HIV during the trial. After the trial ends, an analysis of the data indicates that subjects receiving the vaccine were more likely to develop HIV than subjects receiving a placebo.

One might argue that failing to provide A with access to ART after the trial ends does not harm her because she is no worse-off than before the trial started (Wertheimer 2011). Harm involves making someone worse-off: if you encounter a starving person and provide him with a meal in exchange for his labor, you do not harm him if you do not continue to feed him when his work is finished and he has eaten his meal because he is no worse-off than before you met him. Proponents of post-trial access obligations could respond to this critique by arguing that participants in Case 1 may experience psychological harm as a result of their disappointment and distress at no longer having access to medications. Critics of post-trial access obligations could admit that psychological harm may occur, but argue that this harm is not significant enough to warrant payment for ART indefinitely.

Case 2 is different from Case 1 because it appears that some subjects were made worse-off as a result of their participation, since they developed HIV infection. In this situation, one could argue that subjects who received the vaccine were injured as a result of their participation and that sponsors should compensate them for this injury (see discussion in Chap. 7). Compensation could include free medical treatment, including ART, after the study ends (Lo et al. 2007). It is important to note, however, that this argument does not imply that sponsors have a duty to pay for ART medications for all subjects in the study when it ends; it only supports paying for medications for subjects who can prove that they were injured in this study.

According to the non-exploitation argument, sponsors should pay for post-trial access to ART to taking unfair advantage of research subjects (Sofaer and Stench 2011). In Chap. 5, I argued that underpayment could be exploitative when it denies human subjects a fair share of the benefits of research. A key premise supporting this conclusion was the claim that research with human subjects is exploitative when it denies the participants or host communities a fair share of the benefits of research (Resnik 2003c; Hawkins 2008). Thus, to determine whether failing to pay for post-trial ART treatment is exploitative, we need to consider whether this would deny research subjects or host communities a fair share of the benefits of research

(Resnik 2003c; Wertheimer 2011). The answer to this question depends on how the benefits of research are distributed among the various stakeholders, i.e. human subjects, host communities, investigators, institutions, and sponsors.

Let's first focus on potential exploitation of human subjects. If the sponsor is a private company that expects to reap a huge profit from the study, and the subjects only benefit from treatments received during the study, then one could argue that fairness demands that the sponsor should provide the subjects with additional benefits, such as post-trial access to medications (Hawkins 2008). However, if the sponsor is a government agency or private charity that is conducting research to increase human knowledge and benefit the local population, then its decision to not pay for post-trial access to medications would probably not be exploitative, because it would not be acquiring an unfair share of the benefits. Government agencies and private charities do not profit from research.

Turning our focus to potential exploitation of communities, it is worth noting that local populations often derive significant economic benefits from research. Clinical trials generate high-paying jobs and infuse money into the local economy. Although these economic benefits are significant, proponents of the non-exploitation argument for ART would claim that fairness demands that the sponsor provide additional benefits to the host community, such as funding post-trial ART for research participants (Hawkins 2008). However, this argument for providing post-trial treatment has limited force, because there are many ways that the sponsor or investigator could benefit the host community other than providing post-trial ART to research subjects, such as investing in the community's health care or educational infrastructure, developing medical products or services or services that will be available to the community, or providing low-cost or free medications to all community members. One could argue that community leaders, sponsors, and investigators should decide how to share benefits fairly and that the agreements they reach may or may not include post-trial access to medications (see discussion below). Exploitation of the community would be less likely to occur if the sponsor is a government agency or private charity, because the sponsor would not profit from the research.

According to the reciprocity argument, sponsors should fund post-trial ART for research subjects as quid pro quo payment for their contributions to research. The reciprocity argument is similar to the non-exploitation argument in that it holds that human subjects should receive a fair share of the benefits of research, which includes post-trial access to medications. One might object to this argument by claiming that reciprocity may or may not require that human subjects receive post-trial access to medications, since they might receive meaningful benefits during the conduct of the study, such as access to treatments, ancillary care, or payment.

According to the global justice argument, sponsors should pay for post-trial ART for research subjects to address global injustice (Sofaer and Stench 2011). Some of the most socially disadvantaged people in the world are HIV-infected patients who do not have access to treatment due to limited local health care resources. Sponsors can help address international socioeconomic inequalities by offering to pay for

post-trial ART for resources subjects in resource-poor settings. The reply to this argument is that requiring research sponsors to provide medical treatment for patients in resource-poor settings confuses the goals of research with the goals of human development. One might agree that it would be a good thing if all HIV/AIDS patients in the world had access to ART, yet argue that research sponsors are not morally responsible for achieving this goal. Other stakeholders, such as local governments, international relief organizations, and private charities should deal with social justice issues related to access to HIV treatment. The best way that sponsors can help HIV/AIDS patients is by funding research that is expected to enhance our understanding of the treatment and prevention of this disease. Requiring sponsors to pay for post-trial ART for research subjects would divert their focus and attention from their primary aims.

Switching to arguments against sponsors' obligations to pay for post-trial ART, the first type of argument appeals cost: requiring sponsors to pay for post-trial ART treatment would increase the costs of research in resource-poor settings unreasonably (Sofaer and Stench 2011). The cost of ART varies across the globe, depending on market forces and government price controls. The price ranges from $113 per person per year in South Africa to $400 per person per year in the U.S. (UNAIDS 2013). If a person lives 50 years after a trial has ended, a sponsor might have to pay $5600 to $20,000 from lifetime post-trial access to ART or from $2.3 million $10 million for a clinical trial of 500 subjects. A sponsor of clinical trial might accommodate these higher costs by cutting back on some research activities, which could compromise the scientific and social value of the study; or, worse yet, the sponsor might decide to not fund the study, due to its excessive costs (Wertheimer 2011). Cost would be a significant consideration regardless of the profit/non-profit status of the sponsor: for example private companies would need to decide whether the costs of the study would be justified in terms of expected profits, and government agencies would need to decide whether the costs would be justified in terms of expected public benefits. The NIH, for example, does not fund post-trial access to ART but encourages investigators to work with authorities in host countries and other stakeholders to ensure continued access to care (National Institutes of Health 2005). The NIH's justification for this policy is that it has been legally authorized to fund biomedical research but not treatment (National Institutes of Health 2005).

Proponents of post-trial treatment obligations could respond to this financial argument by suggesting that sponsors could cover the costs of ART medications until a government agency, private charity, or international aid organization picks up the costs. Sponsor-supported post-trial access to treatment would be a temporary bridge until other stakeholders assume this responsibility.

A second argument against sponsors' post-trial treatment obligations is that informing human subjects that they are entitled to receive ART treatment after the study ends might contribute to the therapeutic misconception (see discussion in Chap. 5) by encouraging them to think that the purpose of the study is to provide them with treatment (Sofaer and Stench 2011). Proponents of post-trial access obligations could argue that investigators can help dispel the therapeutic misconception

by making sure that subjects understand the purpose of the study is to develop scientific knowledge, not to provide them with treatment.

A third argument against sponsors' post-trial treatment obligations is that offering human subjects ART after the study ends might constitute undue inducement (see discussion in Chap. 5) to participate in research. HIV-infected participants in resource-poor countries might not be especially susceptible to this form of inducement. Proponents of post-trial treatment obligations could argue that offering treatment to subjects after the study ends would not constitute undue inducement as long as the subjects are able to make intelligent decisions concerning the benefits and risks of the study.

As one can see, there are compelling arguments on both sides of this issue. While most people would agree that investigators, institutions, and sponsors should make arrangements for post-trial access to ART in HIV/AIDS treatment or prevention studies in resource-poor settings, deciding who should cover the costs of ART is controversial. If we approach this issue from the perspective of trust, it is clear that failing to make provisions for post-trial access to ART in resource-poor setting may undermine subjects' and communities' trust in investigators, institutions, and sponsors, since most believe that they deserve post-trial access to treatment. HIV/AIDS patients who no longer have access to ART when a clinical trial ends may feel that they have been abandoned, exploited, and betrayed. Members of the communities in which these patients live may harbor similar feelings. Research sponsors, institutions, investigators, and IRBs should do their best to avoid this negative outcome. Ideally, sponsors should offer to temporarily pay for post-trial ART until local governments and other parties can cover these costs. Priority should be given to providing ART to subjects who have developed HIV as a result of their participation in the study. If sponsors do not have funds to pay for post-trial ART, or paying for treatment outside of a study is not part of their mandate, then investigators and institutions should work with other stakeholders to provide post-trial access to HIV care. They should also inform research subjects about the availability of treatment after the study ends, and they should consult with local community leaders concerning post-trial treatment issues.

8.8 Benefits in Placebo-Controlled Clinical Trials

In the previous chapter we focused on ethical issues related to risks associated with placebo-controlled RCTs. Some have also objected to placebo-controlled RCTs in which there is an effective treatment on the grounds that they fail to offer medical benefits to subjects in the placebo group. According to this critique, it is unethical to conduct a placebo-controlled RCT when there is an effective treatment for the disease because this violates the physician's professional duty to benefit his or her patients (Lurie and Wolfe 1997; Miller and Weijer 2003). In the previous chapter, I argued that enrolling patients in placebo-controlled RCTs when an effective treatment exists is ethical if the subjects provide consent and do not face the risk of

serious or irreversible harm. Some critics of placebo-controlled RCTs have argued that consent and harm minimization are not sufficient: subjects must also benefit from access to effective treatment.

For example, critics argued that the HIV prevention trials discussed in Chap. 1 were unethical because they failed to offer patients in the placebo groups beneficial treatments. These studies did not harm the subjects because they did not require them to forego effective treatment, since no treatment was available locally due to limited health care resources in host nations (Resnik 1998). Critics argued, however, that the physicians nevertheless violated their ethical duty to provide subjects with the standard of care for preventing mother-child transmission of HIV, i.e. treatment with antiretroviral drugs (Lurie and Wolfe 1997). Defenders of the trials responded that physicians were only obligated to provide the local standard of care, not the standard of care that prevailed in the U.S. and other developed countries. Since antiretroviral drugs were not available locally, the physicians did not violate their duty to provide subjects with the standard of care (Resnik 1998).[6] Defenders of the trials also argued that while the studies did not benefit subjects in the placebo groups, they benefitted the host communities and nations by providing important knowledge that led to development of a more affordable method of preventing perinatal HIV transmission (Varmus and Satcher 1997; Wendler et al. 2004).

Critics responded to these arguments by claiming that investigators, institutions and sponsors who failed to provide subjects with the standard of care available outside of the host nation were exploiting the research subjects (Glantz and Grodin 1998; Schüklenk 1998; London 2001). As noted earlier, exploitation of human subjects or communities may occur when there is harm, lack of consent, or an unfair sharing of the benefits of research (Resnik 2003c). Critics argued that the HIV trials exploited human subjects because the subjects in the placebo groups did not receive a fair share of the benefits of research and their ability to consent was compromised, due to their dire circumstances (Schüklenk 1998; Ballantyne 2010). Subjects were too willing to agree to participate in a study in which they might receive placebo instead of effective intervention because no treatment was available locally. Subjects in developing nations would not have consented to studies like these because they would have been able to obtain access to antiretroviral drugs without participating in a research. Defenders of the trials could conceded this point yet argued that the HIV prevention trials provided the host nations and communities with a fair share of the benefits of research because they succeeded in developing an affordable form of prevention that would be available to those nations and communities (Resnik 1998; Wendler et al. 2004). Thus, one could argue that while the trials may have exploited participants in the placebo groups, they did not exploit the host nations or communities (Levine 1998).

If we look beyond this controversy, we can see that this trade-off between benefitting individuals and benefitting society often occurs in research with human subjects. For example, subjects in Phase I drug dosing studies conducted in the U.S. are

[6] For more on the debate about the relevant standard of care, see London (2000).

not likely to benefit significantly from their participation, but society may benefit considerably if these studies lead to the development of a new drugs to treat diseases. Social science surveys may also offer far more benefits to society than they do to human subjects. The main reason why we conduct research with human subjects is to benefit society, not necessarily the participants. Human subjects may also benefit, but research can still be ethical when the benefits largely accrue to society (Emanuel et al. 2000).

Approaching the controversial of HIV prevention trials from the perspective of trust, one could argue that these studies undermined placebo recipients' trust in investigators, institutions, and sponsors, since subjects expected to benefit from participation. Some critics of the trials argued that many of the subjects failed to understand that the trials were not designed to benefit them and that they might receive a placebo (Lurie and Wolfe 1997). While these studies may have undermined subjects' trust, they probably did not undermine the host communities' trust, since host communities benefitted from the research. Moreover, investigators, institutions, and sponsors worked closely with representatives from host communities in designing and implementing the trials (Varmus and Satcher 1997). A meeting convened by the World Health Organization Global Program on AIDS in 1994 concerning the design of these trials included 28 experts from 6 developing and 8 developed nations. One of the local representatives involved in study design, Edward Mbidde, Director of the Uganda Cancer Institute at Makerere University in Uganda, Africa, defended the trials on the grounds that they addressed important health care needs in the host communities (Mbidde 1998).

8.9 Fair Benefits to Host Communities and Nations

A common theme in our discussion of returning individual results, ancillary care, post-trial access to treatment, and clinical trials involving placebos is the idea of providing benefits to host communities or nations. Most bioethicists agree that investigators, institutions, sponsors, and IRBs should take make special efforts to minimize the potential for exploitation when conducting, funding or overseeing research in developing nations (Hawkins 2008). Studies should be designed and implemented so that host communities or nations are likely to receive a fair share of the benefits of the research. The ethical obligation to share benefits fairly takes on special importance when one considers developed nations' history of taking advantage of developing nations in trade, resource extraction, politics, and so on. Since people who live in developing nations are likely to be aware of this legacy of oppression, slavery, and colonialism, they may be especially sensitive to any interaction that appears to be unfair (Hawkins 2008).

Since the 1990s, pharmaceutical companies have outsourced clinical trials to developing nations to take advantage of low labor costs, willing volunteers, and lax regulatory environments (Hawkins 2008). Although the FDA prefers to review data from clinical trials conducted in the U.S., it will accept data from studies conducted

outside the U.S., provided that the trials meet certain conditions, such as conformity with good clinical practices guidelines (Food and Drug Administration 2012). Some developing nations, such as India and China, have actively courted pharmaceutical companies to obtain economic benefits from doing business with them. These trends have important implications for benefit-sharing, since private sponsors may reap significant profits from research conducted in developing nations.

In 2001, investigators, bioethicists, and IRB members from the U.S., Europe, and eight African nations met in Malawi to consider issues related to the sharing of benefits in research with human subjects. Members of this group developed a proposal known as the fair benefits framework. The framework consists of the following key points (Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries 2002, 2004):

- **Collaborative partnership:** investigators, institutions, and sponsors should work with community representatives to develop a plan for benefit sharing; benefits should address the community's needs and concerns.
- **Broad and flexible benefits**: the benefits to the community can take many different forms, such as: making treatments shown to be effective in a study reasonably available to members of the community; providing ancillary care or post-trial access to medications to research subjects; providing health care services or medications to other community members; and developing local health care infrastructure.
- **Transparency**: an independent group, such as the World Health Organization, should collect and publish benefit sharing arrangements to enable host communities to have the information they need to negotiate with investigators, sponsors and institutions.

Although the fair benefits framework was developed to provide guidance for research conducted in developing nations by developed nations, the key points of the proposal would seem to apply to other types of research involving communities. Exploitation could be an issue whenever there is potential for unfair sharing of benefits in research with human subjects. Investigators conducting research in impoverished regions of the U.S. should also consider taking measures to share benefits with local populations or communities (Resnik et al. 2015a). For example, NIEHS investigators who were studying the health impacts of cleanup activities related to the Deepwater Horizon oil spill in the Gulf of Mexico in 2010 were cognizant of the need to provide tangible benefits to the participants. Investigators shared individual research results with volunteers and made referrals to medical care, if appropriate. The investigators became aware of the importance of providing benefits to the subjects as a result of discussions with representatives from the host communities (Resnik et al. 2015a).

8.10 Conclusion

In this chapter I have considered some ethical issues related to providing benefits to human subjects, communities, or nations involved in or impacted by research. I have addressed issues related to research benefits, including sharing individual research results with human subjects, providing ancillary care, enrolling subjects in placebo-controlled clinical trials, and offering benefits to host communities or nations. I have also discussed how sharing benefits with research subjects and host communities is important for promoting trust. While it is ethically desirable to offer benefits to stakeholders involved in or impacted by research with human subjects, beneficence is not an absolute obligation, and must be balanced against other considerations, such as study design, scientific goals, and financial or resource limitations. In the next chapter I will explore ethical issues related to research on vulnerable subjects.

Chapter 9
Vulnerable Subjects

In previous chapters, we have touched on some ethical issues pertaining to research involving vulnerable subjects, such as risks to children and pregnant women/fetuses. In this chapter, we will focus on dilemmas faced by investigators, institutions, IRBs, and sponsors related to research involving vulnerable subjects. In Chap. 2, we noted that the federal regulations include a general requirement for protecting vulnerable subjects (45 CFR 46.111a3, 45 CFR 46.111b) as well as specific requirements pertaining to pregnant women, fetuses and neonates (Subpart B), prisoners (Subpart C), and children (Subpart D). The Helsinki Declaration also provides guidance on research involving vulnerable subjects:

> All vulnerable groups and individuals should receive specifically considered protection. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research (World Medical Association 2013).

Likewise, CIOMS guidelines requires additional protections for vulnerable subjects:

> When vulnerable individuals or groups are considered for recruitment in research, researchers and research ethics committees must ensure that specific protections are in place to safeguard the rights and welfare of these individuals and groups in the conduct of research (Council for the International Organizations of Medicals Sciences 2016:70).

The 2002 and 2016 versions also includes sections which address research involving children, pregnant women, and adults with mental disabilities or diseases that affect decision-making (Council for the International Organizations of Medicals Sciences 2002, 2016). Research regulations an ethical guidance include the following types of additional protections for vulnerable subjects:

- **Justification for including vulnerable subjects in research**. The CIOMS guidelines recommend that a justification be provided for including vulnerable subjects. For example, children should not be included in a study if the research

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objectives can be accomplished by enrolling only adults (Council for the International Organizations of Medicals Sciences 2002, 2016). The federal research regulations require that the selection of research subjects be equitable (45 CFR 46.111a3), which implies that vulnerable subjects should not be unfairly included in research (Mastroianni and Kahn 2001).

- **Limits on research risks**. Federal regulations place limits on the risks that fetuses, neonates, children, pregnant women, and prisoners can be exposed to in research that does not offer them direct benefits (45 CFR 46, Subparts B, C, D).
- **Rules for IRB Composition**. Federal regulations require that an IRB which reviews research on prisoners include a prisoner or prisoner representative (45 CFR 46.304). Commentators have argued that IRBs which review research on mentally disabled people, children, and other vulnerable subjects also should include members with the appropriate background and experience concerning the study population or that they should consult with outside experts (National Bioethics Advisory Commission 1998; Institute of Medicine 2004).
- **Safeguards for Consent**. Federal regulations specify procedures for obtaining consent from the parent(s) and assent from the child in pediatric research (45 CFR 46 Subpart D). The National Bioethics Advisory Commission (1998) recommends that investigators follow procedures for assessing decision-making capacity in mentally disabled or ill adults and identifying surrogate decision-makers for subjects who are incapable providing consent. In some cases, an IRB might require independent monitoring of the consent process to protect vulnerable subjects.
- **Safeguards for privacy/confidentiality**. Additional protections for privacy and confidentiality might be appropriate for research involving students or employees to prevent their professors or employers from having access to private information that could be used against them (Bonham and Moreno 2008; Resnik 2016b).
- **Benefit sharing**. Some ethical guidelines include procedures for sharing benefits with research subjects or host communities/nations to minimize the potential for exploitation (see discussion in Chap. 8).

Before discussing specific ethical issues it will be useful to define the term "vulnerable subject"[1] since this plays a key role interpreting and applying regulations and guidance and thinking about the ethical issues.

9.1 Who or What Is a Vulnerable Subject?

The federal research regulations do not explicitly define "vulnerable subject" but they include an explicit definition: "When some or all of the subjects are likely to **be vulnerable to coercion or undue influence**, such as children, prisoners, pregnant

[1] Some commentators use the term "vulnerable population" instead of vulnerable subject. I prefer to use the term "vulnerable subject" because it coincides with phrasing used in the federal regulations and reminds us that we are protecting the rights and welfare of individuals, not groups.

women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects 45 CFR 46.111b [emphasis added]." This implicit definition focuses on vulnerability to coercion or undue influence, which suggests that vulnerability is related to the concept of consent: vulnerable subjects are people who may not be able to provide valid consent because they are susceptible to coercion or undue influence.

Some of the categories of vulnerable subjects mentioned in this passage, e.g. older children, prisoners, adults with mental disabilities or diseases that affect decision-making, would seem to fit this definition. Although older children cannot provide legally valid consent for research participation, their concurrence (or assent) is still required (see discussion in Chap. 5). Children may be susceptible to parental pressure to participate in research (Wendler 2010). Although prisoners are capable of providing legally valid informed consent, they may face pressures from guards or prison administrators to participate in research and they may be offered inducements, such as the promise of early release for good behavior (Bonham and Moreno 2008).[2] Adults with mental disabilities or diseases that affect decision-making may face pressure from caregivers, investigators, or others to consent or assent to research participation (see discussion below).

Although older children, prisoners, and adults with mental disabilities or diseases that impair decision-making seem to fit this definition, one might question whether pregnant women, fetuses, or younger children should be considered vulnerable to coercion or undue influence (Schonfeld 2013). The fetus is not vulnerable to coercion or undue influence because it is incapable of making decisions. One might argue that the fetus is vulnerable because it is dependent on the mother and susceptible to harm in utero (Schonfeld 2013). Likewise, neonates, infants, and very young children are not vulnerable to coercion or undue influence because they do not make decisions. Their vulnerability is related to their dependency on adults and susceptibility to harm.

Furthermore, there is nothing about gestation as a medical condition that makes pregnant women vulnerable to coercion or undue influence (Grady and Denny 2008). Although a pregnant woman's cognitive and emotional functioning may be impacted by hormonal influences and bodily changes, we normally assume the pregnant women are perfectly capable of making medical decisions and consenting to participation in research (Schonfeld 2013). To assume otherwise is to take a sexist view of pregnancy. While it is appropriate to require additional safeguards for pregnant women participating in research to protect fetuses from harm, pregnant women should not be classified as vulnerable subjects (Schonfeld 2013).

Individuals with mental disabilities or illnesses that can impair decision-making have traditionally been classified as vulnerable subjects, due to their susceptibility to coercion or undue influence (Rosenstein and Miller 2008). Although the *Belmont*

[2] Prior to revisions of the federal research regulations pertaining to research with prisoners in 1978, pharmaceutical companies frequently used prisoners in Phase I drug studies. See Hornblum (1999).

Report (National Commission 1979) discussed the vulnerabilities of research subjects with mental disabilities or illnesses, the federal research regulations do not include any special protections for these individuals. In the absence of federal policy on research involving individuals with mental disabilities or illnesses, many investigators, institutions, and IRBs follow the recommendations developed by the National Bioethics Advisory Commission (1998) and the CIOMS guidelines (2002, 2016).

Macklin (2003) argues that subjects in extreme poverty, such as people living in developing nations, should be considered vulnerable because they are susceptible to exploitation. These subjects may be easily exploited in research because they are socioeconomically disadvantaged and lack access to health care. They may therefore be willing to enroll in studies that unfairly distribute the benefits and risks of research (see discussions of exploitation in Chaps. 5 and 8). Viewing subjects in extreme poverty as vulnerable can encourage investigators and IRBs to take steps to protect them from exploitation, according to Macklin (2003). Denny and Grady (2007) and Levine (2008) critique the notion that subjects in extreme poverty should be considered vulnerable. They argue that these subjects often can make sound decisions and they can refuse to participate in studies that distribute benefits and risks unfairly. Classifying such subjects as vulnerable could exclude them from research that offers benefits to the participants or their communities. Denny and Grady (2007) and Levine (2008) argue that investigators can take measures to protect the rights and welfare of subjects in extreme poverty even if these participants are not classified as vulnerable.

Brody (1998b) and Menikoff (2009) consider extremely ill patients as vulnerable research subjects. Very ill patients may be vulnerable because (a) they may have symptoms related to their illness (such as pain, emotional and physical distress) that impair judgment and decision-making; (b) they may be susceptible to undue influence from their physicians or family members; and (c) they may be disposed to agree to enroll in exploitative studies that do not distribute benefits and risks fairly. For example, a person with terminal cancer may be willing to try an experimental drug recommended by his or her doctor even though the chance of benefitting from the treatment is slim and the drug has harmful side effects.

Moskop (1998) argues that military personnel should be viewed as vulnerable research subjects due to their increased risks and susceptibility to coercion and undue influence. Although Department of Defense has adopted the Common Rule (45 CFR 46) for its research, military personnel may face significant pressures to participate in research (Bonham and Moreno 2008). For example, during the 1991 Persian Gulf War, U.S. military personnel were ordered to receive investigational vaccines and drugs to protect them from biological and chemical weapons. Military personnel who refused to take the vaccines or drugs were dishonorably discharged. The U.S. military argued that administering vaccines and drugs to soldiers was treatment and not research, and that its policy was justified out of military necessity. In 1990, the FDA granted the Department of Defense a waiver to allow military health care professionals to administer these medications to soldiers (Howe and Martin 1991). Critics, argued, however, that administering the drugs and vaccines to the soldiers was research, not treatment, because these medications had not been

tested or approved for these particular uses (Howe and Martin 1991). Many Gulf War veterans claimed that they developed adverse reactions from the drugs, such as nausea, cramps, vomiting, skin rashes, difficulty breathing and memory loss. A Senate committee investigating soldier's complaints found that they often were not informed about the risks of the drugs or vaccines they were taking (Leary 1994).

O'Mathúna (2010) and Ferreira et al. (2015) argue that victims of floods, earthquakes, hurricanes, tornados or other natural disasters should be regarded as vulnerable research subjects, due to psychological stress, trauma, and other factors that can impact their decision-making. NIEHS investigators who were studying the health impacts related to cleaning up the Deepwater Horizon oil spill considered many of the research participants to be vulnerable subjects, due to trauma, stress, poverty, language barriers, and lack of access to health care (Resnik et al. 2015a, see further discussion in Chap. 8).

Other potential vulnerable subjects include students who are participating in research projects conducted by their professors, employees participating in research conducted by their employers, individuals who lack language proficiency, racial or ethnic minorities, and elderly people (Sachs and Cassel 1990; King 1998; Resnik and Jones 2006; Bonham and Moreno 2008; Lo and Garan 2008; Rogers and Lange 2013; Resnik 2016b).

Levine et al. (2004) argue that the concept of vulnerability has become so vague and malleable that it has little value in discussions of ethical and policy issues in research with human subjects. They claim that so many categories of people have been added to the list of vulnerable subjects that calling someone "vulnerable" has no meaningful implications for research protections and oversight. Furthermore, classifying certain types of subjects as vulnerable may stereotype them and prevent them from participating in beneficial research (Levine et al. 2004). Levine et al. (2004) propose that bioethicists, investigators, and IRBs should stop using the concept of vulnerability and instead focus on aspects of research protocols which require special scrutiny to protect the rights and welfare of research subjects.

While I agree with Levine et al. (2004) that the concept of vulnerability is in dire need of clarification, I think it still has some value in ethical and policy debates about research with human subjects, because it focuses the investigator's and IRB's attention on the appropriateness of providing additional protections for some types of human subjects. Following Coleman (2009), I suggest that we can distinguish between three types of vulnerability: (a) vulnerability related to impaired decision-making, (b) vulnerability related to risks; and (c) vulnerability related to the potential for exploitation. An individual must have at least one of these three types of vulnerability to be considered vulnerable. Some individuals (e.g. children) may meet all three of these conditions (see Table 9.1). Classifying certain types of subjects as vulnerable should only be the beginning of the ethical discussion, however. The purpose of the classification is to call attention to special concerns related to protecting the rights and welfare of these subjects (Levine et al. 2004; Coleman 2009). Depending on the type of vulnerability identified by the classification, subjects may need additional protections related to decision-making, risk exposure, or the potential for exploitation. For example, fetuses require additional protections

Table 9.1 Vulnerable subjects

Type of subject	Type of vulnerability
Fetuses/pregnant women[a]	Risk, exploitation
Neonates	Risk, exploitation
Infants and young children	Risk, exploitation
Older children and adolescents	Risk, decision-making, exploitation
Mentally disabled or ill adults	Risk, decision-making, exploitation
Seriously ill patients	Risk, decision-making, exploitation
Elderly	Decision-making
Prisoners	Decision-making, exploitation
Impoverished people	Exploitation
Racial/ethnic minorities	Exploitation
Military personnel	Risk, decision-making, exploitation
Disaster victims	Decision-making, risk
Students	Decision-making, risk
Employees	Decision-making, risk, exploitation
Individuals lacking language proficiency	Decision-making

[a]Additional protections apply to pregnant women to protect the fetus

related to risks and the potential for exploitation but not decision-making. Socioeconomically disadvantaged people may require additional protections related to decision-making and the potential for exploitation. Subjects with limited English proficiency may need consent forms and other documents translated into their preferred language. Subjects who are illiterate may need someone to read the consent form to them (Resnik and Jones 2006).

9.2 Research Involving Children

Children are the first type of vulnerable subject we will discuss in this chapter.[3] In Chap. 7, we considered some issues related to research on children when we discussed the topic of minimal risk. We noted that under the Common Rule, an IRB may approve three types of pediatric research: (a) research that does not offer direct benefits to the subjects but is minimal risk; (b) research that offers directs benefits to the subjects; and (c) research that does not offer direct benefits to the subjects but is minor a increase over minimal risk and is likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR 46.404, 405, 406). Pediatric research which does not fit into these three categories must be reviewed and approved by a special federal panel (45 CFR 46.407).[4]

[3] Although I have identified 15 different types of potentially vulnerable subjects, I will focus on the three types which have generated the most debate, i.e. children, mentally disabled or ill adults, pregnant women/fetuses.

[4] As noted in Chap. 2, the EPA has its own regulations pertaining to research involving children. The EPA does not allow funded-investigators to conduct any research that intentionally exposes children to environmental agents. See Resnik (2007c).

Most commentators agree that it is ethical to enroll children in research that offers them direct medical benefits (i.e. beneficial research[5]), but there is considerable controversy about enrolling children in non-beneficial research, especially research that exposes them to more than minimal risks. We allow competent adults to enroll in risky, non-beneficial research (such as Phase I trials on healthy volunteers) because they can make their own decisions concerning their risk exposure. But since children cannot make such decisions, it is incumbent on their parents or guardians to make these decisions for them.

In the 1970s, Protestant theologian Paul Ramsey and Catholic theologian Richard McCormick engaged in a public debate about including children in non-beneficial research. After they defended opposing views on the topic in the *Hastings Center Report*, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research invited them to present their views at its meetings (Jonsen 2006).

McCormick (1974) published an essay in *Perspectives in Biology and Medicine* in which he argued that children can participate in research with their parents' proxy consent. Parents can consent to research that one may reasonably presume that a child would want to consent to, if he or she were capable of providing consent. McCormick argued that consent can be presumed for beneficial clinical research, because a child would want to have access to medical treatment. McCormick (1974, 1976) also stated that children can participate in non-beneficial research because all people in society have duties of beneficence and their participation may offer important benefits to other children and society as a whole. Parents can give their proxy consent for such research if one presumes that children would want to fulfill these moral obligations and contribute to society. McCormick (1976) proposed a risk threshold for enrolling children in non-beneficial research, which later became known as the minimal risk standard.

Ramsey (1976) strongly objected to McCormick's view because it treats children as moral agents who are obligated to contribute to society. Ramsey argued that we should not ascribe duties of beneficence to children because they are developing persons and not fully moral agents. If we presume that children have duties of beneficence, we are in danger of allowing parents to harm or exploit their children for the good of society. Parents do not have the right to consent to non-beneficial research for their children, because they are morally bound to act in the best interests of their children. Parents can consent to beneficial research for their children because participation is likely to be in the child's best interests. A parent cannot legitimately consent for research which offers his or her child no benefits and exposes the child to risks because such research is not in child's best interests (Ramsey 1970).

[5] Some refer to this as "therapeutic" research but this terminology is misleading because it conflates research and therapy (Levine 1988). As noted in Chap. 2, research and therapy are distinct conceptual categories: research aims to develop knowledge, while therapy aims to help patients. I prefer to use the term "beneficial" research to indicate that the research offers the subject the prospect of direct, medical benefits.

McCormick (1976) admitted that children are not are not fully moral agents but asserted that they are morally developing persons who may still learn important lessons if we allow them to participate in socially beneficial activities, such as research. Participating in research can indirectly benefit children by contributing to their moral education, which is consistent with the child's best interests.

After much deliberation, the National Commission sided with McCormick. The federal research regulations reflect McCormick's view that it is acceptable to enroll children in some types of non-beneficial, low-risk research (Jonsen 2006). However, the issues that McCormick and Ramsey addressed persist to this day (Kopelman 2000; Institute of Medicine 2004; Jonsen 2006; Ross 2006; Wendler 2010, 2013). The issue boils down to a conflict between protecting children from risks and promoting children's health and well-being. Is it ethical to expose some children to risks to benefit other children? That is the key question.

The trust-based approach offers us some potential insight into this moral conflict. One could argue that the best way to promote trust in research is to follow pediatric research risk standards which are comparable to relevant community standards for children's risks, because investigators would not be exposing children to more risks than they would likely be exposed to outside of the research context, and they therefore would not be violating the community's trust. The risks of daily life in the definition of minimal risk (see discussion in Chap. 7) is one type of community standard for children's risk exposure in non-beneficial research (Wendler et al. 2005). However, one might argue that it may be acceptable to expose children to more than minimal risks in non-beneficial research in some cases if we can identify a comparable community standard for these risks. As noted above, the federal research regulations allow children to be exposed to more than minimal risks in some types of research likely to yield important results for pediatric health. One might argue that community service activities are a comparable community standard for such risks, since these activities promote the good of society but expose children to some risks without providing them with any direct medical benefits (Wendler 2012).

For example, Habitat for Humanity, which builds homes for indigent people, allows children aged 16 or older to participate in construction work and those 14 or older to participate in exterior painting or landscaping (Habitat for Humanity of San Antonio 2017). The American Red Cross (2017) allows healthy children as young as 16 to donate blood, with parental permission. Many hospitals and nursing homes accept high school-age volunteers (see University of North Carolina Medical Center 2017). Children 13 or older also often participate in sandbagging efforts when rivers flood (KPLR 2013). Most of us would agree that it acceptable for parents to include younger children in low-risk community service activities, such as collecting donations to food banks or raising money for charitable organizations, such as the Boys Scouts or Girl Scouts.

These examples reinforce McCormick's point that parents may permit their children to participate in non-beneficial research to help society and teach children about the value of helping others. Thus, one might argue that participation in non-

medically beneficial research promotes the child's best interests in some cases.[6] This argument for allowing children to participate in non-beneficial, more than minimal risk research makes the most sense when the children are old enough to learn moral lessons from participating in research, e.g. they are 10 years old or older. This argument has less force when children are younger than 10 years old, since they are not likely to have the intellectual or emotional maturity needed to comprehend the value of helping others. However, Wendler (2012) argues that even a very young child who participates in non-beneficial research may come to embrace his or her contribution to society when he or she is old enough to appreciate it.

If we accept that the general idea that children may participate in non-beneficial research that is more than minimal risk, the next question we need to address is whether there should be some limits on these risks. To better understand the issues, it may be useful to consider an actual case involving pediatric more than minimal risk research.

On November 17, 2005, the FDA's Pediatric Advisory Committee met to consider whether to approve a pediatric study titled "Gonadotropin Releasing Hormone Agonist Test in Disorders of Puberty" proposed by University of Chicago pediatrician Robert Rosenfield (Food and Drug Administration 2005).[7] The purpose of the study was to test the effectiveness of leuprolide in diagnosing disorders of puberty, such as premature onset and delayed onset puberty. Other methods of diagnosing puberty disorders were not reliable or too expensive to be reimbursed by insurers. The study included a group of children with puberty disorders and a group of normal controls (age 7–18). Normal controls would be paid $150 but the diseased children would not be paid because they would be receiving treatment. Study procedures included (Food and Drug Administration 2005):

- 36-h admission to the hospital's clinical research unit;
- Placement of venous catheter for obtaining blood samples totaling 150-240 ml (5–8 ounces), depending on the weight of the child;
- Injection of a single dose leuprolide (10 micrograms per kilogram of body weight);
- X-rays to measure bone age;
- DNA testing;
- Administration of oral iron to prevent anemia.

Enrolling the subjects with puberty disorders was not in dispute, since they would undergo the same tests and procedures even if they were not in the study. For them, the study would be considered beneficial research approvable under 45 CFR 46.405 (Food and Drug Administration 2005). Enrolling the normal controls presented a problem, since they would be exposed to more than minimal risks with no

[6] See Kopelman (1997) for further discussion of the best interests standard in parental decision-making.

[7] Although the FDA has its own research regulations it follows Subpart D of the Common Rule for overseeing pediatric research. The study fell under the FDA regulations because the sponsor was seeking approval for the leuprolide test.

compensating medical benefits. The study could not be approved under 45 CFR 46.406, because the normal volunteers did not have a disease or condition. To approve the study under 45 CFR 46.407, the federal panel had to determine that:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
(ii) the research will be conducted in accordance with sound ethical principles;
(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians (45 CFR 46.407).

The committee assessed the risks of administration of leuprolide, the insertion of an indwelling catheter, the loss of blood, and the potential psychological harm of a 36-h hospital admission for the children. Committee members all agreed that the risks were more than minimal (Food and Drug Administration 2005). Public comments reviewed by the committee expressed concerns about the risks of a leuprolide injection and problems with the consent process. Several professional societies endorsed the study and said that it was necessary to obtain data from healthy controls to evaluate the effectiveness of the leuprolide test. The committee determined that the study could be approved if it was modified as follows:

(a) The results of the leuprolide test should not be disclosed to the normal control subjects or their parents because these results would be clinically uncertain and might convey the false impression that the child was abnormal, which could cause psychological harm;
(b) The consent and assent documents should provide more information about the risks of the leuprolide injection and more clearly state that the normal controls would not receive any medical benefits (Food and Drug Administration 2005).

Were the risks for the normal controls in this study reasonable in relation to the value of the knowledge expected to be gained? Were the risks excessive? Let's consider some of the most significant ones:

Risks of leuprolide. Leuprolide decreases levels of some hormones produced by the testes and ovaries. According to Drugs.com (2017), common side-effects of the drug include: "Breast tenderness; constipation; decreased sexual desire or ability; difficulty sleeping; hot flashes or sweating; infection (fever, chills, sore throat); nausea or vomiting; pain, redness, or swelling at the injection site." Rare side-effects include: "Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); blood in the urine; burning, numbness, tingling, or weakness; fainting; fast, slow, or irregular heartbeat; mental or mood changes (e.g., anxiety, delusions, depression, nervousness); new or worsening bone pain; paralysis; seizures; severe dizziness or light-headedness; severe drowsiness; severe headache; shortness of breath; swelling of the hands, ankles, or feet; symptoms of heart attack (e.g., chest, jaw, or left arm pain; numbness of an arm or leg; sudden, severe headache or vomiting; vision changes); symptoms of high blood sugar (e.g., drowsiness;

fast breathing; flushing; fruit-like breath odor; increased thirst, hunger, or urination); symptoms of stroke (e.g., confusion, one-sided weakness, slurred speech, vision changes); trouble urinating or inability to urinate; and vision changes (Drug.com 2017). It is important to note, however, that most of these risks only occur with long-term use of the leuprolide; a single injection of the drug is not likely to produce significant side-effects (Drugs.com 2017).

Risks of a venous catheter: infection, bleeding, and discomfort (see Chap. 7).

Risks of a 36-h hospital stay: risk of a hospital-acquired infection; psychological stress, discomfort, boredom.

Risks of collecting 150-240 ml of blood: anemia, dizziness, fainting, shortness of breath.

Risks of x-ray: negligible for the level of exposure to ionizing radiation in the study (see Chap. 7).

While the risks of the study clearly should be treated as more than minimal, none of them stand out as egregiously risky. The study did not involve a significant risk of an SAE or death and included plans to control and minimize the medical risks (Food and Drug Administration 2005). One might argue that the most significant risk of the study was the 36-h hospital admission, which could be psychologically stressful for the younger children in the study and their parents and would expose them to hospital-acquired infections. However, parents could withdraw their children from the study if they were unable to tolerate the hospital stay.

To determine whether these risks were excessive, we can compare them to the risks of other community service activities we allow children to participate in, such as constructing houses for Habitat for Humanity. The risks of construction work are wide-ranging and can be significant. Some types of potential harm include: cuts and bruises, sunburn, muscle strains, broken bones, exposure to hazardous chemicals, heat exhaustion, and dismemberment, permanent disability, or death. As noted in Chap. 7, construction work has a mortality rate 18.76 of deaths per 100,000, making it 18 times riskier than restaurant work. If we consider construction work to be the upper bound of risk-exposure for non-beneficial pediatric research, then the leuprolide study would probably fall well below this limit.

It is important to note, however, that Habitat for Humanity requires children to be at least 16 years old before they can participate in construction work. As noted above, other service organizations also place age restrictions on children's participation because children below a certain age might not be capable of performing some physically demanding or mentally challenging tasks. Children younger than 16 years old, for example, may develop anemia if they donate blood. However, service organizations probably also have age restrictions because there is a widespread social consensus that children's risk exposure in socially beneficial activities should be proportional to age. One reason why many people accept this idea is that older children are more capable of making their own decisions concerning risks than younger children. Although older children cannot give legally valid consent to risky activities, they are approaching the age of consent, and their decision-making abilities are

generally better than those of younger children.[8] Additionally, older children may appreciate being given the opportunity to participate in adult activities and to contribute to society.

These foregoing ethical reflections suggest that the upper bound for children's risk exposure on non-beneficial research should be a function of age: older children may be exposed to greater risks in non-beneficial research than younger children. Putting all of these points together, I propose the following guideline for children's exposure to risks in non-beneficial research:

> **Maximum level of risk for children participating in non-beneficial research: Risks not greater than the risks children typically are exposed to in comparable age-appropriate community service activities**.

Under this standard, 17-year-olds could face risks not greater than the risks of working for Habitat for Humanity but 7-year-olds could face risks not greater than the risks of soliciting contributions for a charitable organization.

As mentioned above, the age range for the leuprolide study was 7–18 years old. Applying my age-based risk guideline to this study, one could argue that younger normal controls should have been excluded from the study, since they would have faced risks greater than those typically encountered by children in comparable age-appropriate community service activities. 12–18 years old would have been a more reasonable age range for normal controls in this study, assuming that there is not a compelling scientific justification for including younger children.

Some might object that my age-based risk guideline may prevent investigators from conducting some research that could have important benefits for children's health. I agree that this could happen, but keep in mind that the guideline is only a guideline, and there could be justifiable exceptions to this rule. However, the burden of proof should fall on those who propose non-beneficial studies that would involve risks exceeding those of comparable age-appropriate public service activities.

Before concluding this section, it is important to note that protectionist pediatric research policies may have had an overall negative impact on children's health. Most new drugs used to treat diseases that affect the general population are tested in adults and infrequently in children. As a result, most drugs used to treat children are prescribed on an off-label basis (Bazzano et al. 2009).[9] Off-label prescribing can pose serious problems for children's health, since drugs may affect children and adults differently, which means that dosing by weight can be unreliable. Also, some drugs have very different effects in children and adults. For example, some drugs used to treat attention deficit hyperactivity disorder (ADHD) help children to maintain focus and attention but may induce anxiety and agitation in adults (Bazzano et al. 2009).

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[8] Parents of teenagers may disagree, of course!

[9] When the FDA approves a drug, it approves it to treat specific populations with specific diseases. It also approves a dosage and route of administration for the drug. Once a drug is on the market, physicians are legally permitted to prescribe for un-approved uses, i.e. off-label.

There are a couple of reasons why drugs are infrequently tested in children. The main reason is economic: medications used to treat chronic illnesses that affect mostly adults may generate higher profits for pharmaceutical companies than medications used to treat or prevent childhood diseases. An adult with hypertension may need to take a drug for the rest of his life, whereas a child with a bacterial ear infection may only need to take an antibiotic for a week, and only a few doses of vaccine may be needed to prevent a childhood disease. A company may decide that it would rather develop a drug that someone will take for many because of its higher profit potential. To encourage private companies to invest in R & D related to children's health, the U.S. Congress passed the Best Pharmaceuticals for Children Act in 1997. The law grants companies an additional 6 months of market exclusivity if they test a drug on children and allows the FDA to require pediatric testing in some cases (National Institutes of Health 2017).

Another important reason why drugs are infrequently tested in pediatric populations is that, as we have seen, research regulations include additional protections for children. Although the regulations permit companies to conduct clinical trials that offer benefits to pediatric subjects and society, IRBs may be hesitant to approve such studies, given protectionist attitudes toward including children in research (Mastroianni and Kahn 2001). Some clinical studies may require investigators to recruit a population of healthy controls who may be exposed to more than minimal risks with no compensating medical benefits. As we saw above, such studies can only be approved by a special federal panel. Investigators may decide to forego conducting these types of studies, given the difficulties with obtaining approval.

9.3 Research Involving Adults with Mental Disabilities or Diseases that Impair Decision-Making

Adults with mental disabilities or diseases that impair decision-making need additional protections in research because they may have compromised ability to consent to research participation (National Bioethics Advisory Commission 1998; Chen et al. 2002; Rosenstein and Miller 2008). A dementia patient may not have adequate memory or reasoning skills to make competent decisions. Likewise, an adult with psychosis may also have impaired cognitive abilities, especially if his or her condition is not well-controlled. As noted above, the federal research regulations do not include any special rules for protecting mentally disabled or ill adults in research or place any limitations on the risks that these subjects may be exposed to in research. One reason why the federal regulations may not include additional protections for mentally disabled or ill adults is that these subjects are a highly diverse group: some mentally ill or disabled adults may have good decision-making abilities, while others may not. Also, some may be able to make decisions under certain conditions (e.g. when their condition is controlled by medication) but not others (e.g. when their condition is not well-controlled).

Most commentators agree that adults with mental disabilities or diseases that may impair decision-making should not be included in research unless there is a sound scientific justification for including them (National Bioethics Advisory Commission 1998; Council for International Organizations of Medical Sciences 2002, 2016). As noted in Chap. 2, the National Commission (1979) warned against including some subjects in research because of their "easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied (p. 6)." Mentally disabled or diseased adults seem to belong to this category. That being said, there are often good scientific reasons for including mentally disabled or diseased adults in research. For example, researchers may want to learn more about psychosis, depression, dementia, drug addiction, traumatic brain injury, and other diseases or conditions that can impair decision-making. Also, some adults may develop mental illnesses or disability while they are participating in long-term studies.

Assuming that there are often sound scientific reasons for including adults with mental disabilities or diseases that may impair decision-making in research, the next question that arises is how best to protect their rights and welfare. As noted above, forms of protection that most commentators endorse are safeguards for ensuring that consent is valid. Research protocols that include adults with mental disabilities or diseases that may impair decision-making should include procedures for assessing the subject's decision-making capacity (DMC) and identifying a legally authorized representative (LAR) if the subject is incapable of providing consent (National Bioethics Advisory Commission 1998; Chen et al. 2002). To identify an appropriate LAR, investigators must be familiar with local laws and customs, since these determine who can fulfill this role. Some potential LARs include: a guardian (if the subject has been adjudicated incompetent), a health care agent (if the subject has executed a health care power of attorney form), an immediate family member, or another family member or close friend (National Bioethics Advisory Commission 1998). When an LAR is used, adult subjects should provide their assent, if they are capable of doing so. The LAR may assist with decision-making or make the decision, depending on the subject's level of DMC (Chen et al. 2002).[10]

In some cases, adults with declining mental abilities (e.g. patients with Alzheimer's or Parkinson's disease) may sign advance directives for research participation when they are still competent. Research advance directives are similar to other advance directives, such as living wills, in that they allow competent adults to express their preferences concerning certain decisions before they lose their mental faculties. Research advance directives promote the competent adult's autonomous decision-making by allowing him or her to decide whether to participate in research. When the adult can no longer consent, LARs may consent on the adult's behalf in accordance with his or her previously expressed preferences,

[10] DMC is usually not an all or nothing trait and may vary, depending on the individual's mental status, emotional temperament, medical condition, etc. A high degree of DMC may be required to make complex and risky decisions, whereas a lower degree of DMC may suffice for making simple, low-risk decisions. See Chen et al. (2002).

unless the adults objects to participating (i.e. does not assent). The NIH encourages patients at its Clinical Center to execute research advance directives (Muthappan et al. 2005).

One issue that may arise in assessing DMC is that investigators or members of the research team may have a conflict of interest that could bias their judgment. Since investigators are likely to be interested in enrolling subjects in a study in order to meet recruitment goals, they may bias their assessment in favor of affirming the subject's DMC, so that he or she can consent to research participation (National Bioethics Advisory Commission 1998; Chen et al. 2002). To minimize the potential for bias, investigators could use a formal DMC assessment tool or have an independent party assess DMC (Chen et al. 2002). Since the latter option may be inconvenient for investigators and research subjects and increase the costs of the study, it should be used only for more than minimal risk research (Chen et al. 2002).

Most commentators agree that enrolling adults with mental disabilities or diseases that may impair DMC in minimal risk research does not raise any special ethical concerns because it does not expose them to significant risks. Also, enrolling these subjects in medically beneficial research does not raise special ethical concerns because it offers them benefits (such as treatment) which compensate them for risk exposure. Most of the ethical debate has focused on enrolling adults subjects with impaired DMC in more than minimal risk, non-beneficial research when they have not executed a research advance directive (Chen et al. 2002; Rosenstein and Miller 2008). The ethical issues with enrolling these adults in more than minimal risk, non-beneficial research are similar to those that arise with enrolling children in these types of studies, since the research subjects have not consented to participation.

In the previous section, I argued that we use community service activities as a comparable community standard for setting an upper bound for risk exposure in non-beneficial pediatric research. If we follow this line of reasoning, then we should look for a comparable community standard for enrolling adults with mental disabilities or diseases with impaired DMC. We do allow adults with mental disabilities or diseases that may impair decision to participate in service activities that may expose them to more than minimal risks. For example, the American Red Cross (2017) does not routinely exclude individuals with mental disabilities or diseases from donating blood. A woman with Down syndrome has donated gallons of blood over the years (Talk Down Syndrome Talk 2013). One might argue that adults with mental disabilities or diseases that may impair decision-making can benefit psychologically from participating in community service activities, such as research, because it may provide them with a sense of self-esteem by allowing them to contribute to society. The Down syndrome woman who has donated blood, for example, takes pride in being able to save lives (Talk Down Syndrome Talk 2013).

Although there are some good reasons for allowing adults with mental disabilities or diseases that impair DMC to participate in non-beneficial, more than minimal risk research, one might argue that investigators and IRBs should be cautious about enrolling these subjects in these studies, because the potential for coercion, undue influence, and exploitation is great. It is easy to imagine how an investigator might easily convince a mentally disabled or diseased adult with impaired DMC to

participate in a study that places him or her at risk without compensating medical benefits. As noted earlier, the National Commission (1979) warned against this type of situation. If a mentally disabled individual were to suffer a severe injury or die in a non-beneficial medical experiment, this could have a detrimental impact on the public's trust in research. Given these concerns, one could argue that the default position should be that adults with mental disabilities or diseases that impair DMC should not participate in more than minimal risks, non-beneficial research unless they have executed an advance directive expressing a desire to do so or there are compelling scientific reasons for including them in research. An IRB may require independent monitoring of the consent and assent processes to ensure validity.

9.4 Research Involving Pregnant Women

We will preface our discussion of the ethical issues pertaining to research involving pregnant women by noting, that prior to the 1990s, U.S. investigators and research sponsors routinely excluded all women, not just pregnant women, from clinical trials (Dresser 1992). The reasons for excluding women from clinical trials were twofold. First, many were concerned about the legal liability arising from harms to the fetus from in utero exposures to drugs, radiation, or other interventions or procedures. The thalidomide tragedy of the 1950s and 1960s was still fresh on investigators' and sponsor's minds. Thousands of children whose mothers had taken this drug to control nausea during pregnancy were born with severe birth defects, such as stunted limbs. The tragedy affected mostly European children, because the FDA was still reviewing thalidomide when the adverse effects of the drug surfaced (Grady and Denny 2008). Investigators and sponsors believed that, to be on the safe side, all women should be excluded from clinical trials, because female research subjects might have false negative pregnancy tests, and even if a woman were not pregnant during the study, the effects of the drug might linger and cause fetal harm if she subsequently became pregnant. Second, many believed that the female reproductive cycle was an uncontrolled variable that could make it difficult to interpret clinical trial data. Investigators and sponsors were concerned that female hormones, such as estrogen and progesterone, might interact with medications and confound clinical trial data (Dresser 2001).

During the 1980s, women's health advocates argued that investigators and sponsors were unfairly excluding women from clinical research and that these policies had a negative impact on women's health. Since women and men are physiologically different, results from studies of the safety and efficacy of a treatment in men might not readily apply to women's health care. Physicians might not know whether a drug affects women differently than men, or how to dose the drug in women, for example. Women's health advocates also argued that diseases that affect mostly women, such as breast cancer, were understudied (Dresser 2001). In response to these concerns, Congress passed laws requiring the NIH and FDA to develop policies for including women and minorities in research (Grady and Denny 2008). The

NIH requires that funded-investigators include women and minorities in research unless there is a legitimate scientific or ethical reason for exclusion (National Institutes of Health 2001). For example, women do not need to be included in a study of prostate cancer, because they do not have prostates. Pregnant women may be excluded from more than minimal risk studies that do not offer benefits to the women or fetus to comply with federal regulations (Grady and Denny 2008).

Although the U.S. has made considerable strides toward enrolling women in clinical trials, many of the concerns that led to the development of exclusion policies still remain. Fetuses are extremely susceptible to harm from exposures to drugs in utero. Drugs can harm the fetus by: (1) crossing the placenta and acting directly on the fetus; (2) impairing the function of the placenta and restricting blood flow to the fetus; (3) causing the uterus to contract prematurely; and (4) lowering the woman's blood pressure which can reduce blood flow to the fetus. Two to three percent of birth defects result from medications taken during pregnancy (Gunatilake and Patil 2017). Investigators and sponsors are justifiably hesitant to include pregnant women in clinical trials, given the potential for fetal harm. As a result of the reluctance to include pregnant women in clinical drug trials, less than 10% of the medications approved by the FDA contain information in the labelling pertaining to the risk of birth defects (Centers for Disease Control and Prevention 2016). Given the lack of knowledge about how drugs affect the developing fetus, many clinicians advise women to refrain from taking any unnecessary medications during pregnancy and to taper off medications prior to attempting to conceive (Centers for Disease Control and Prevention 2016; Gunatilake and Patil 2017).

Despite these concerns, investigators and sponsors might decide that it would be important to include pregnant women in a drug study to promote women's health. Some women must take medications during pregnancy to manage illnesses, such as hypertension, diabetes, asthma, epilepsy, or depression, which could threaten their life or health if untreated (Gunatilake and Patil 2017). Lack of knowledge about how these medications affect pregnant women or their fetuses could lead to unsafe prescribing practices. Before initiating a drug study that will include pregnant women, investigators should evaluate the evidence about potential teratogenic effects of the drug from FDA databases, human observational studies, and animal experiments (Grady and Denny 2008). If studies indicate that a drug causes birth defects in laboratory animals, it would be unwise to conduct a clinical trial of the drug that enrolls pregnant women. It may also be imprudent to include pregnant women in a clinical trial of a drug which belongs to the same chemical class of a drug known to cause birth defects in animals or humans. For example, thalidomide belongs to a class of drugs known as immunomodulatory agents (MedlinePlus 2017). Given the known teratogenic effects of thalidomide, investigators should avoid enrolling pregnant women in clinical trials of immunomodulatory agents. If pregnant women will participate in a clinical trial of a drug, the protocol should include procedures for evaluating the impact of the drug on the fetus during the study and afterwards. If data indicate that a drug may be adversely impacting the fetus (e.g. an ultrasound shows that the placenta or fetus is not growing normally),

investigators could withdraw the woman from the study. In cases of suspected severe birth defects, the woman could consider having an abortion.

If investigators decide to exclude pregnant women from a study, they should require fertile[11] females to take a pregnancy test prior to enrollment. The test could be repeated during the study if appropriate. Women who become pregnant during the study would be withdrawn. Investigators should also ask fertile female participants to use an effective form of birth control while in the study and refrain from attempting to conceive a child for a limited period of time after the study ends to ensure that the body has eliminated the drug (Grady and Denny 2008).

As a side note, while much of the ethical and regulatory discussion concerning research-related birth defects has focused on the pregnant woman, it is important to realize that a father's toxic exposures may also impact the fetus. Some studies have shown that paternal genetic or epigenetic damage caused by drugs, toxic chemicals, pesticides, or radiation can be transmitted to offspring (Cordier 2008; Anderson et al. 2014). Investigators should keep this in mind when designing clinical trials and informing men about potential risks to their children from exposures to radiation or drugs.

9.5 Conclusion: Protection vs. Access

In our discussion of the ethical issues of research involving vulnerable human subjects, protection vs. access has emerged as common theme. Most of the early discussion of vulnerable subjects emphasized the importance of protecting them from harm, coercion, undue influence, and exploitation (Mastroianni and Kahn 2001). The *Belmont Report* set the tone for this discussion by calling for additional protections for vulnerable subjects and warning investigators about including subjects in research because of their convenience or manipulability (National Commission 1979). Federal agencies heeded this advice by adopting special protections for children, prisoners, and pregnant women/fetuses involved in research.

However, in the 1980s, it became clear to many that these research policies were adversely affecting the health of protected populations (Mastroianni and Kahn 2001). As noted above, women's health advocates argued that policies that excluded women from clinical trials were having an adverse impact on women's health, and children's health advocates have argued that protectionist policies have adversely impacted the health of children. Although not classified as vulnerable subjects by research regulations, during the 1980s and 1990s, HIV/AIDS patients pressured the federal government into giving them greater access to experimental medications being tested in clinical trials. As a result, the FDA developed rules that allow manufacturers to make experimental drugs which have undergone Phase I safety testing available to seriously ill patients who are not enrolled in clinical trials (Darrow et al. 2015).

[11] E.g. the woman has not had a hysterectomy and not gone through menopause.

Research policies pertaining to vulnerable subjects straddle the horns of a dilemma pertaining to exclusion/protection on the one hand and inclusion/access on the other. Policies that exclude individuals from research to protect them from harm, exploitation, or coercion/undue influence may adversely impact the health of the group to which they belong (Mastroianni and Kahn 2001; Resnik 2007c). At its core, this dilemma embodies the moral tension between protecting individuals and promoting the common good which, as we have seen in this book, arises frequently in research.

Some have viewed the protection vs. access issue through the lens of social justice (Kahn et al. 1998; Mastroianni and Kahn 2001). The principle of justice stated in the Belmont Report holds that the benefits and burdens of research should be distributed fairly (National Commission 1979). As noted above, federal research regulations require that the selection of research subjects be equitable, i.e. fair (45 CFR 46.111a3). One could argue that policies which exclude certain groups of vulnerable subjects from research are unfair because they prevent members of that protected class from obtaining the benefits of research (Kahn et al. 1998). Conversely, one could also argue that it would be unfair to impose risks on vulnerable research subjects in order to benefit members of their groups. Thus, the justice argument could cut both ways, depending on whether one is concerned with unfairly denying benefits to a group or unfairly burdening research subjects with risks.

How would the approaches to distributive justice discussed in Chap. 3—libertarianism, utilitarianism, and Rawlsian egalitarianism—address these issues? Briefly, we could say that libertarians would have no objections to policies that exclude certain groups from research participation or include certain groups, as long the recruitment process is procedurally fair, e.g. researchers obtain valid, informed consent from the subject or LAR. Utilitarians would support policies which are likely to maximize benefits to society and minimize harms. For example, if excluding pregnant women from clinical trials is likely to produce more overall good than bad for society, then utilitarians would favor such a policy. If the policy is likely to have the opposite effect, then utilitarians would disfavor it. Rawlsian egalitarians would favor policies that promote the well-being of the least advantaged members of society, such as socioeconomically disadvantaged people, racial or ethnic minorities, and children. A Rawlsian could argue, for example, that excluding children from clinical research is unfair because it does not promote the interests of children, who are some of society's least advantaged members. However, it is important to note that this paragraph contains only a rough sketch of how these different theories of justice might apply to inclusion/exclusion policies, and more critical reflection is needed to refine the discussion.[12]

From the perspective of trust, significant harm to vulnerable subjects participating in research can undoubtedly erode trust in investigators, institutions, sponsors, and the research enterprise. As we saw in Chap. 2, research regulations and ethical guidelines were developed, in part, to restore the public's trust in research, especially research involving vulnerable subjects. However, members of the public may also

[12] See Powers (1998).

lose confidence in investigators, institutions, sponsors, and the research enterprise if they feel that research is not addressing their needs and concerns (Mastroianni and Kahn 2001). Women's health advocates, for example, pressured the federal government not only to include women in clinical trials but also to fund more research on women's health (Dresser 2001). Likewise, HIV/AIDS patients succeeded in convincing federal agencies to allocate more money toward research on HIV/AIDS (Dresser 2001). Thus, trust can be a double-edged sword, favoring both protection and access.

Perhaps the best way of moving forward with respect to policy development, protocol design, and research review is to promote awareness not only of the need to protect vulnerable subjects but also of the importance of conducting research that enhances the health and well-being of the groups to which they belong. Decisions related to excluding or including certain classes of vulnerable subjects from research should be made with an eye toward how those choices will impact human subjects as well as members of protected groups. Investigators, IRBs, institutions, and sponsors should carefully balance these conflicting values when planning, reviewing, and implementing research involving vulnerable subjects (Mastroianni and Kahn 2001; Meltzer and Childress 2008).

Chapter 10
Research Integrity

In Chaps. 5, 6, 7, 8, and 9 I have focused on specific issues related to research with human subjects, such as informed consent, confidentiality, risks, benefits, and vulnerability. In this chapter, I will shift gears and examine a topic that indirectly impacts human subjects but which is nevertheless very important: research integrity. Research integrity (or responsible conduct of research, RCR) has to do with following ethical and legal standards in the conduct of research (Shamoo and Resnik 2015). These include rules pertaining to research with human and animals subjects as well as those concerning the conduct of science itself, such as norms for recording, reporting, analyzing, sharing, publishing and interpreting data; assigning authorship; disclosing and handling conflicts of interest; working with collaborators, students, and trainees; reviewing manuscripts and grants; managing financial and other resources; and investigating allegations of misconduct (Shamoo and Resnik 2015). This chapter will consider some RCR issues which have an important bearing on research with human subjects. But first, I will explain why investigator integrity is essential to research with human subjects.

10.1 The Importance of Integrity in Research with Human Subjects

Investigator behavior is probably the single most important factor in protecting the rights and welfare of human subjects. Regulations and guidelines have little utility if investigators ignore them. IRB review and oversight is also ineffective if the investigator does not comply with the approved protocol and consent process as well as ethical and legal standards for the conduct of research. Investigators (and research staff members) have direct contact with human subjects and therefore have the greatest opportunity to either help or harm them. IRBs, institutions, and sponsors must therefore trust that investigators will act responsibly. Chapter 2 described

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several cases (e.g. Poisson, Poehlman, Hwang, and Wakefield) in which investigator misbehavior harmed human subjects or placed them at undue risk.

A recent episode at Duke University demonstrates how misconduct can directly harm research subjects. In November 2015, the Office of Research Integrity (ORI), which oversees the integrity of NIH-funded research, found that former Duke University investigator Anil Potti had included false data in one NIH grant application and 9 published papers. As part of the settlement, ORI required Potti to retract the papers and agree to supervision of his federally funded research for a period of 5 years (Office of Research Integrity 2015). Earlier that year, Duke University had settled a lawsuit brought by eight participants in Potti's oncology clinical trial who claimed they were harmed by his fraudulent research (Stancil 2015).

Potti had been working with Joseph Nevins on cancer genomics in the early 2000s. They hypothesized that one could use a tumor's genomic signature to predict its response to chemotherapy. In 2006, they published a paper in *Nature Medicine* describing a predictive model that they had developed using computer programs and publicly available genomic data for the tumors (Potti et al. 2006). Shortly after the paper appeared in print, two statisticians, Keith Baggerly and Kevin Coombes, detected errors in the model and could not replicate the results. They contacted Potti and Nevins about issues they had with the paper and published a critique in the same journal (Coombes et al. 2007). Potti and Nevins responded to these critiques and insisted that their model worked. In 2008, Bradford Perez, a 3rd year medical student at Duke University who was working under Potti and Nevins, found problems with their predictive model and discovered that it had not been independently validated. Perez was worried that patients could be harmed because Potti and Nevins were preparing to begin clinical trials based on their research. Perez shared his concerns with university administrators, who encouraged him to work with Potti and Nevins to deal with these issues. They expressed the view that the problems he found amounted to a scientific disagreement rather than misconduct and warned him that he could damage his own career if he brought charges against his supervisors (Goldberg 2015). In 2009, Baggerly and Combes learned that clinical trials had begun at Duke. They published another critique of Potti's research and expressed their concerns to the Duke IRB. The IRB temporarily suspended the clinical trials in order to review the research but then allowed them to start again. In July 2010, *The Cancer Letter* reported that Potti had falsely stated he was a Rhodes Scholar on his curriculum vita and grant applications submitted to the NIH and American Cancer Society (Goldberg 2015). Shortly thereafter, the IRB suspended Potti's clinical trials again and Duke launched a misconduct investigation. In 2012, Potti resigned his position at Duke and took a job at the North Dakota Cancer Center.

Looking beyond this extraordinary case, harms to human subjects or rights violations can also occur as a result of less dramatic transgressions, such as:

- Enrolling a subject in a study who does not meet the inclusion criteria;
- Using unqualified staff to perform research procedures;
- Performing an inadequate review of the literature related to one's research;
- Using an invalid methodology or experimental design;

- Failing to adequately protect confidentiality;
- Not disclosing important information during the consent process;
- Failing to carefully monitor the health of subjects in a clinical study;
- Not reporting adverse events or other problems in a timely fashion.

Investigator behavior also plays a key role in promoting trust in research with human subjects. The cases discussed in Chap. 2 show how misbehavior that harms human subjects can undermine the trust that human subjects, communities, and the members of public place in investigators, institutions, sponsors, and the scientific enterprise. Societies have developed regulations, guidelines, and oversight systems to control investigator behavior and thereby protect human subjects.

Misbehavior that does not directly harm human subjects may nevertheless negatively impact society's trust in research if it leads to fraudulent, erroneous, or biased data or results that cause harm to society or increase the risk of harm. For example, Wakefield's study linking the MMR vaccine to autism lowered vaccination rates in the U.K. and other countries, and therefore may have increased infections of measles or other childhood diseases for which there is a vaccine. Merck's exclusion of some cardiovascular risk data from the VIGOR study may have harmed people who took Vioxx because they did not know some of the risks of the drug. If these risks had been fully disclosed to the public, fewer people may have taken the drug and, therefore, fewer may have been harmed. (See fuller discussion of this case below.) Although Poisson's alteration of his patient's medical records did not skew the overall results of the clinical trial, it easily could have if he had changed more records. Conflicts of interest (discussed below) are a significant concern in research because they may increase the risk of bias or misbehavior (Shamoo and Resnik 2015).

Misbehavior that does not harm human subjects or society may still undermine trust if it produces useless results or wastes public resources. One of the main justifications for exposing human subjects to risks is that the study is expected to yield knowledge that benefits society (Shamoo and Resnik 2015). If investigators fabricate or falsify data, then their research may not produce useful results, which would undercut its ethical justification and waste public resources. Mismanagement of research funds can also waste public resources and undermine trust.

Misbehavior may also erode investigators' trust in each other, which is crucial for the advancement of science (Whitbeck 1995). Research involves many types of social interactions between and among scientists (Hull 1988). Some of these include: working together in laboratories or research groups, collaborations among researchers in different groups, peer review, and publication. For these social interactions to work, scientists must be able to trust each other to follow certain standards of behavior (Shamoo and Resnik 2015). They must be able to trust that: they can rely on published research results; collaborators will not steal their ideas, data, or methods; they will receive proper credit for their accomplishments; reviewers will evaluate their work fairly and respect the confidentiality of the peer review, etc.

10.2 Misconduct in Research

The most serious violations of ethical or legal standards in research are classified as misconduct (Shamoo and Resnik 2015). The U.S. government defines research misconduct as: "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results…misconduct does not include honest error or differences of opinion (Office of Science and Technology Policy 2000:76262)." This definition, which is accepted by numerous federal agencies, including the NIH, NSF, and FDA, focuses on three types of misbehavior: fabrication, falsification, or plagiarism (FFP). Fabrication is "making up data or results and recording or reporting them," falsification is "manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record," and plagiarism is "the appropriation of another person's ideas, processes, results, or words without giving appropriate credit (Office of Science and Technology Policy 2000:76262)."

Federal agencies decided to focus on FFP because they viewed broader definitions of misconduct, some of which included the category "other serious deviations" as too vague (Resnik 2003a). However, other countries use definitions of misconduct that go beyond FFP. Resnik et al. (2015c) studied the science policies of the top 40 countries ranked by total research funding. 22 (55%) of these countries had national misconduct policies. While all of these countries included FFP in the definition of research misconduct, most went beyond these categories and included other types of misbehaviors, such as: unethical authorship other than plagiarism (54.6%); unethical publication practices, such as duplicate publication (36.4%); failing to disclose a significant conflict of interest (36.4%); unethical peer review (31.8%); interfering with a misconduct investigation (27.3%), poor record-keeping (27.3%); forms of deception other than FFP, such as manipulating data (27.3%); serious deviations (22.7%); violating confidentiality (22.7%); and serious violations of human or animal research regulations (22.7%). In a separate study of 183 of the top U.S. academic institutions ranked by total research funding, Resnik et al. (2015b) found that 59% use a definition of research misconduct that goes beyond FFP. Included in these definitions were: other serious deviations (45.4%); significant violations of research regulations, such as animal or human subjects regulations (23.0%); misusing confidential information in peer review or other aspect of research (15.8%); interfering with a misconduct investigation (14.8%); unethical authorship other than plagiarism (14.2%); other forms of deception, such as data manipulation (13.1%); and theft or misappropriation of property (10.4%).

Misconduct investigations are legal proceedings in the U.S. and other countries. The ORI has developed policies and procedures that institutions are required to follow when they perform misconduct investigations involving NIH-funded research, but most institutions apply these to all research, regardless of the funding source (Shamoo and Resnik 2015). Research institutions are required to have a research integrity official (RIO) who receives formal allegations of misconduct. If the RIO determines that an allegation meets the definition of misconduct and is genuine, he

or she will appoint a committee to conduct an inquiry to determine whether there is enough evidence to support an investigation. If the inquiry committee concludes that an investigation is warranted, the RIO will appoint another committee to conduct an investigation. The investigation committee will obtain evidence by reviewing research records and other materials and interviewing witnesses. The committee will decide whether the evidence shows that the accused party (i.e. the respondent) has committed misconduct. A finding of misconduct must be supported by a preponderance of evidence, i.e. probability > 50%. Misconduct must be committed intentionally, knowingly, or recklessly (Office of Science and Technology Policy 2000). The RIO will act on the Committee's findings and recommend a punishment if misconduct is found. Sanctions may include: termination of the respondent's employment, demotion, increased supervision of the respondent's work during a probationary period, education in RCR, or a letter of reprimand.

If the research is federally-funded, the institution will report its findings to the appropriate agency. The ORI reviews findings for NIH-funded research. The federal agency may accept the institution's findings, ask for additional evidence or clarification, or conduct its own investigation. If the agency reaches a finding of misconduct, it will usually require the investigator to forego federal research funding for a period of time (sometimes indefinitely) and to correct the publication record (if appropriate) (Shamoo and Resnik 2015). Although researchers rarely face criminal or civil penalties for misconduct, Eric Poehlman served a year and a day in a federal prison and was required to pay the government $180,000 (see Chap. 2).

Institutions are required to follow rules for legal due process when conducting misconduct inquiries and investigations. Respondents are permitted to obtain legal counsel, interview witnesses, and review the evidence. They can also appeal misconduct findings to a federal court. To protect the reputations of the parties, institutions are required to maintain confidentiality during misconduct proceedings. However, sometimes deliberations or findings are unlawfully leaked to the press. ORI publishes cases on its website once it has made official findings of misconduct (Shamoo and Resnik 2015).

Scientific journals have adopted policies for dealing with misconduct allegations (Resnik et al. 2009, 2015d). However, their legal authority to investigate allegations of misconduct is limited. Editors will usually refer such matters to the authors' institutions for resolution. While an investigation is ongoing, the editors may publish an expression of concern, pending the outcome. If there is an official finding of misconduct, editors will usually retract the article, with or without the permission of the authors. Editors may face difficult ethical dilemmas when dealing with alleged misconduct. On the one hand, they have a duty to the journal's reputation and the integrity of the research record. On the other hand, they have a duty to not falsify accuse innocent people of wrongdoing. They may also be concerned about being sued for libel by authors. The Committee on Publication Ethics (2012) has developed some guidelines for editors and journals for handling misconduct cases.

The incidence of misconduct in research is thought to be rare. Fanelli (2009) conducted a systematic review of 21 misconduct surveys and found that 1.97% of scientists had admitted to fabricating or falsifying data or committing plagiarism at

least once in their careers. However, 14.2% said they had observed someone else committing misconduct. Both of these percentages may not reflect the true rate of misconduct. The self-reported rate (1.97%) may underestimate the actual rate because researchers may not be willing to admit that they have committed misconduct, even if their confidentiality is protected. The observed rate (14.2%) may overestimate the actual rate of misconduct because people who claim to have observed misconduct may not have enough evidence to determine whether it has occurred, and some respondents to surveys may observe the same act of misconduct, which may result in double-counting. Even if the rate of misconduct is as low as 2% or less, it still represents a serious threat to the integrity and trustworthiness of research that needs to be addressed (Shamoo and Resnik 2015).

10.3 Noncompliance

The Common Rule requires institutions to have written procedures for prompt reporting of "unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance (45 CFR 46.103b5)." Serious or continuing noncompliance could qualify as research misconduct under federal policies if it involves FFP. As noted above, many academic institutions and some countries classify serious noncompliance with human research regulations as misconduct (Resnik 2015a, b). The NIH's intramural human research protection program defines serious noncompliance as noncompliance that increases the risks of the study or causes harm, decreases benefits, compromises the integrity of the research, or invalidates study data (National Institutes of Health 2016b). Some types of serious noncompliance could include: conducting human subjects research without obtaining IRB approval or when approval has expired, failing to obtain informed consent, significantly deviating from an IRB-approved protocol, fabricating or falsifying data, poorly supervising staff members, or breaching confidentiality.

Investigations of noncompliance in research with human subjects are administrative proceedings which are not nearly as legalistic as misconduct investigations. Anyone involved in research (i.e. investigators, staff, subjects) may report noncompliance. Investigators often report their own noncompliance, which they may discover through a self-audit or a report from a staff member. External audits (routine or for-cause) may also uncover noncompliance (National Institutes of Health 2016b). The IRB receives reports of noncompliance and investigates allegations. The IRB may obtain assistance from an ad hoc committee, administrative staff, or special experts (National Institutes of Health 2016b). If the noncompliance involves an allegation of research misconduct, then it will also be referred to the RIO for review, as occurred in the Potti case (above). The IRB is authorized to take the steps necessary to protect human subjects from potential harm while it is reviewing noncompliance issues. For example, the Duke IRB temporarily suspended Potti's clinical trial to protect human subjects while it was reviewing the research. If the IRB makes a find-

ing of noncompliance, it may recommend further action, such as: terminating or suspending the study; amending the study; additional education or training for the investigator or staff; requiring the investigator to develop policies and procedures to prevent noncompliance from occurring again; or requiring the investigator to inform subjects about the noncompliance if it impacts them. An investigator may ask an IRB to reconsider its findings or disciplinary actions (National Institutes of Health 2016b).

10.4 Whistleblowing in Research

Although federal regulations and institutional policies mandate protection for individuals who report noncompliance, misconduct, or other serious problems with research, whistleblowers still may encounter difficult ethical and personal dilemmas when deciding whether to make allegations (Malek 2010). Even if a whistleblower is not fired or demoted, he or she may face intimidation or harassment from supervisors, colleagues, or administrators. He or she may also develop a reputation as a troublemaker. Institutional officials who do not intimidate or harass whistleblowers may still ignore or minimize their concerns, which occurred when Perez raised issues with Potti's research. If a whistleblower is a graduate student or postdoctoral fellow whose research is supported by grants, he or she may lose funding if his or her supervisor is found to have committed misconduct or serious noncompliance. In some cases, a whistleblower may need to transfer to another laboratory or academic institution to continue his or her research (Malek 2010). Even if whistleblowers are not likely to suffer any adverse career consequences from reporting misconduct or noncompliance, they still may be wary of making an allegation because they want to avoid the stress and time-demands associated with the investigation. Misconduct investigations can last for several years and can be stressful for all parties involved, not just the respondents (Shamoo and Resnik 2015).

Because institutions have a great deal at stake in misconduct cases, such as their reputations or research funding, there is an inherent conflict of interest (discussed below) when they investigate misconduct. University officials may be hesitant to bring charges of misconduct against well-established, prestigious investigators because they do not want to lose grant dollars or face public backlash (Shamoo and Resnik 2015). Although regulations and policies require that members of committees investigating misconduct should have no conflicts of interest, conflicts be difficult to avoid, especially when many of the people involved know each other personally and professionally. To encourage whistleblowers to report allegations of misconduct or noncompliance, many institutions permit anonymous reports. However, it is not be possible to guarantee anonymity if the whistleblower is asked to testify as a witness (Shamoo and Resnik 2015).

10.5 Preventing Misconduct and Noncompliance

While it is important to report and investigate misconduct and noncompliance, prevention is even more important. Prevention can head-off problems before they occur and avoid the damage to human subjects, investigators, institutions, and the scientific enterprise that often results from significant violations of ethical or legal standards in research. To understand how to prevent misconduct and noncompliance, it is important to be familiar with its causes. Some of the causes of misconduct and non-compliance include (Institute of Medicine 2002a, b; Shamoo and Resnik 2015; Dubois et al. 2016):

- Pressures to produce results or publish;
- Poor supervision of subordinates;
- Poor communication;
- Lack of awareness or understanding of research rules;
- Lack of education or mentoring in research ethics and compliance;
- Conflicts between different roles in research (e.g. clinical vs. scientific);
- Conflicts of interest (see discussion below);
- Cultural differences concerning ethical standards;
- Personal conflicts among researchers and staff;
- Poor leadership.

Some forms of prevention may therefore include:

- **Policy development**: Institutions should develop policies related to research integrity issues. The policies should define expected standards of behavior and establish procedures for reporting, investigating, and adjudicating misconduct, noncompliance, and other significant problems in research. Institutions should inform investigators and research staff about their policies and keep them abreast of changes. They should also publicize their policies on websites (Institute of Medicine 2002a, b; Shamoo and Resnik 2015).
- **Education**. Institutions should educate investigators, research staff, students, trainees, and administrators about RCR topics, such as misconduct, compliance, data management, conflicts of interest, etc. RCR education and training should take place when an individual takes a position at an institution or matriculates, as well as at regular intervals subsequently (e.g. annual updates). Researchers who work with human subjects should have special instruction in the relevant regulations, policies, and guidelines (Institute of Medicine 2002a, b; Shamoo and Resnik 2015).
- **Mentoring**. Investigators mentor their students and trainees in research ethics. Mentoring involves teaching by example and through informal discussions. For example, a clinical investigator could mentor a medical student by showing her how to keep research records or explaining to her how the IRB submission process works. Junior faculty members can also benefit from mentoring from senior faculty (Institute of Medicine 2002a, b; Shamoo and Resnik 2015).

- **Leadership**. Institutional leaders should affirm their commitment to research ethics and compliance through their words and deeds. They should stress the importance of following ethical and legal standards for the conduct of research in their communications with investigators, students, trainees, staff, and administrators. Leaders who set a bad example through their questionable behavior or indifference to research integrity may encourage corruption, misconduct, noncompliance, and other ethical and legal problems (Shamoo and Resnik 2015).
- **Auditing**. Institutions should regularly audit research records, including data, case reports, and informed consent documents. Auditing can discourage misconduct and noncompliance and catch problems at the early stages, before they become worse (Shamoo 2013; Shamoo and Resnik 2015).
- **Administrative support**. Institutions should provide adequate administrative support for research ethics and compliance activities, including staff members who work with the IRB as well as officials who can consult with researchers, students, and trainees on ethical or legal issues. Many institutions have an upper-level administrator whose job is to oversee ethics and compliance activities (Institute of Medicine 2002a, b; Shamoo and Resnik 2015).
- **Accreditation**. The Association for Accreditation of Human Research Protections Programs (AAHRPP) accredits institutions which conduct, support, or review research with human subjects. AAHRPP has established standards pertaining to research oversight, policy development, education, administrative support that applicants must meet to receive accreditation. AAHRPP has accredited hundreds of organizations since 2001 (Association for Accreditation of Human Research Protections Programs 2012a, b). Accreditation can promote compliance with ethics policies and guidelines and signal the institution's commitment to integrity in research.

10.6 Conflict of Interest

A conflict of interest (COI) in research occurs when an investigator has a financial, professional or other interest which is likely to affect his or her tendency to fulfill his or her professional, ethical or legal obligations (Thompson 1993; Shamoo and Resnik 2015). COIs can impact adherence to professional, ethical, or legal duties by influencing judgement, decision-making, or behavior (Davis 1982; Resnik 2007a). COIs therefore increase the risk of misconduct, noncompliance, corruption, or other problems in research (Shamoo and Resnik 2015). Some examples of COIs include:

- **Financial**: ownership of stock of equity; intellectual property; receipt of speaking fees or honoraria from a research sponsor; paid consulting arrangements;
- **Professional**: relationships with students, mentors; collaborators;
- **Personal**: relationships with family of friends;
- **Political**: involvement in political organizations or interest groups.

Institutions may also have COIs if the organization or its leaders have financial or other interests which are likely to impact institutional decision-making. For example, if a private company is giving a major gift to a university or supporting millions of dollars of research, institutional leaders may make decisions that favor the company and compromise the university's academic mission or scientific integrity. Commentators on the Gelsinger case (discussed in Chap. 2) were concerned that the University of Pennsylvania had financial interests related to the research which could have impacted its oversight of the gene therapy experiment (Resnik 2007a).

A COI is different from a conflict of obligation or duty (Resnik 2007a). For example, a physician who is enrolling patients in a placebo-controlled clinical trial in which an effective therapy already exists has a conflict between his duties as a physician and his duties as a researcher, but not a COI, if he has no significant interests at stake. A conflict of obligation could become a COI if the investigator's interests favor one obligation over another.

A COI is also different from a conflict of commitment, which occurs when investigators have different professional commitments competing for their time and effort. For example, a university professor who spends a significant amount of time consulting for industry might not have enough time to meet her teaching, advising, or research obligations. Conflicts of commitment can usually be handled by proper time management. Most universities have policies concerning the amount of time and effort that one may devote to outside activities, such as private consulting (Shamoo and Resnik 2015).

COIs, especially financial ones, have increased in research since the 1980s, due to the growing commercialization of science and the complex web of interactions between academic institutions and private industry (Krimsky 2003). Two key pieces of legislation passed in the early 1980s, the Bayh-Dole Act and the Technology Transfer Act, allowed scientists to patent inventions developed using federal funds and to transfer those inventions to universities. Congress passed these laws to encourage transfer of technology from the public to the private sector and to spur economic development.

In the 1980s, private companies, especially pharmaceutical, biotechnology, and information technology firms, began investing more money in research and development (R &D) in their own laboratories and on academic campuses. At the same time, government support of non-military scientific research stagnated, due to budgetary constraints related to economic downturns and increased spending on defense and entitlement programs. R & D funding in the U.S. shifted from about 50% industry and 50% non-industry (government, university, and private philanthropy) in the 1970s to about 65% industry by the beginning of the twenty-first century (Shamoo and Resnik 2015).

In response to dwindling government support, universities have been seeking R & D contracts with private companies and accepting large corporate gifts, which they have used to develop research infrastructure. Today, many universities have buildings, laboratories, or endowed professorships named after industry donors and some have corporate campuses (Krimsky 2003). Universities also began to seek

income from intellectual property developed by faculty. Universities established technology transfer offices to help scientists apply for patents and to manage the institution's intellectual property, including copyrights. A university scientist who patents an invention is normally required to transfer the patent to the institution in exchange for a share of the royalties (usually around 50%). Universities also provided faculty with legal and financial support needed to form start-up companies to commercialize products and services (Shamoo and Resnik 2015). Faculty members began to rely more on private funding to support their research and they accepted money from industry for consulting, writing, or lecturing. Faculty members and universities also acquired stock or equity in private companies that sponsor R &D. Some universities formed private foundations to manage these investments and dole out venture capital for faculty companies (Krimsky 2003).

COIs are an ethical concern in human subjects research for several reasons. First, COIs may bias data or results (United States Congress 1990; Resnik 2007a; Shamoo and Resnik 2015). There is a growing body of evidence on the relationship between financial interests, industry funding, and research outcomes (Hampson et al. 2008). Numerous studies have demonstrated the existence of a funding effect in science: studies sponsored by the manufacturer of a product are more likely to favor the product than studies sponsored by an independent organization, such as a government agency (Bekelman et al. 2003; Sismondo 2008a). For example, Cho and Bero (1996) found that 98% of studies published in symposium proceedings with drug company support reported results favorable to the drug under investigation, compared to 79% without company support. Stelfox et al. (1998) found that among studies of calcium channel-blocking drugs with authors with ties to drug companies, 96% reported findings supportive of the drugs under investigation, while studies with authors without industry ties were neutral (60%) or critical (37%). Friedberg et al. (1999) found that 95% of articles with industry funding reported positive results for cancer treatments as opposed to 62% without industry funding. Ridker and Torres (2006) found that 65% of articles with industry funding reported favorable results for new cardiovascular drugs as opposed as opposed to 39.5% without industry funding. Studies have also shown that financial COIs are associated with research outcomes. Friedman and Richter (2004) reviewed 398 original articles published in the *New England Journal of Medicine* and the *Journal of the American Medical Association* in 2001 and found a strong association between one of more authors having a financial COI (such as stock or fees for consulting or speaking) and positive findings, e.g. evidence that a treatment is safe and effective. Articles that disclosed a financial COI were 2.3 times more likely to report positive findings than those that did not disclose a financial COI (Friedman and Richter 2004). Friedman and Friedman (2016) also found a strong association between financial COIs and research outcomes in 373 original articles published in occupational and environmental health journals in 2012. Articles disclosing financial COIs were 4.31 times more likely to report negative findings, e.g. no evidence that a chemical or agent is dangerous.

There are a several plausible explanations of the effect of financial interests on scientific research, i.e. the funding effect (Krimsky 2003). The first is that company

funding decisions can impact outcomes. For example, drug companies are required to conduct preliminary studies pertaining to a drug's chemistry, pharmacology, and toxicity before proceeding to clinical trials. Thus, when a company decides to fund a clinical trial it already has some data suggesting the drug may be safe and effective. Also, companies may decide to withdraw funding from studies that are not yielding favorable results. While it is important to counteract this potential source of bias, for example, by using public funds to sponsor independent studies, the fact that funding decisions made by companies can affect outcomes does not support the thesis that these outcomes are inherently tainted or unreliable (Resnik 2007a; Resnik and Elliott 2013).

A second explanation is that a company may decide not to publish results which go against its financial interests. Although many would regard data suppression as unethical under most circumstances, companies are not legally required to publish their research and can treat data and results as trade secrets. For example, if a company sponsors a clinical trial comparing its drug to competing drugs and the trial does not show that its drug is better than the competitors, it could decide to suppress the results of this study. It would still need to report the data to the FDA, but the FDA would treat the data as confidential. A salient example of this phenomenon occurred in 1995, when Boots Pharmaceuticals forced University of San Francisco pharmacologist Betty Dong to withdraw a paper from publication in the Journal of the American Medical Association. Boots had sponsored Dong's study, which compared its hypothyroidism drug Synthroid (levothyroxine) to generic alternatives. The study found that Synthroid was not superior to the generic drugs and that the U.S. government could save millions of dollars per year by switching Medicaid and Medicare patients with hypothyroidism from Synthroid to a cheaper generic drug. Dong had signed a contract with Boots giving the company the right to prevent her from publishing the research without the company's written approval. Dong withdrew her paper after the company threatened to sue her for violating the agreement. Fortunately, the company eventually decided to allow Dong to publish the study in the New England Journal of Medicine, but only after it had published an article favorable to Synthroid (Shamoo and Resnik 2015).

Sometimes a company's decision to suppress data can place human subjects at risk. For example, Nancy Olivieri and her collaborators at the University of Toronto (UT) and Toronto General Hospital (TGH) published a paper in the New England Journal of Medicine in 1995 which found that deferiprone is effective at treating the thalassemia and has few side effects. The drug's manufacturer, Apotex, sponsored their research. Olivieri soon noticed that many of her patients had increasing iron levels that placed them at risk of heart failure or death. In May 1996, she decided to inform TGH's research ethics board (REB) about this problem but the company told her not to do this. After discussing the issue with representatives from Apotex, Olivieri decided to submit a report to REB. Within three days, the Apotex terminated the research and withdrew all supplies of the drug from the hospital's pharmacy. The company also threatened to sue Olivieri if she told her patients, regulatory agencies, or researchers about her concerns with the drug. After receiving additional threatening letters from the company, Olivieri withdrew a presentation on the drug

she had submitted to a scientific meeting. In 1998, Apotex, which was in the middle of negotiation large donations to UT and TGH, pressured these institutions to take action against Olivieri, which they did. The institutions tried to discredit Olivieri and her research and took steps to dismiss her from her position. Fortunately, some of Olivieri's colleagues intervened on her behalf prevented her from being dismissed (Olivieri 2003).

A third explanation is that researchers or sponsors may sometimes deliberately bias results to promote their financial interests. Although published studies indicate that fraud is rare in science (Fanelli 2009), when it does occur significant financial interests are often at stake (Shamoo and Resnik 2015). For example, Poehlman admitted that financial pressures influenced his behavior. Wang was probably also impacted by the money and the prestige he expected to gain from his research. Most of the evidence concerning research misconduct in the U.S. has come from surveys of government-funded researchers or official findings of misconduct published by the NIH or NSF, and we know very little about misconduct cases, patterns, or trends in privately funded research (Shamoo and Resnik 2015). However, it is likely that the incidence of misconduct in privately-funded is not very different from the incidence in publicly-funded research.

A fourth explanation is that companies may decide not to publish all the data from a study. A notable example of data omission occurred in research on Merck's drug Vioxx (rofecoxib). In 1999, the FDA approved Vioxx for the treatment of arthritis and pain. Merck claimed that one of the benefits of the drug is that it produces fewer adverse gastrointestinal (GI) effects than other non-steroidal, anti-inflammatory drugs commonly used to treat arthritis and pain. Vioxx generated an estimated $2.5 billion in annual sales. In 2001, researchers published the results of a Merck-sponsored clinical trial, named VIGOR, in the New England Journal of Medicine. VIGOR showed that Vioxx produces fewer GI side effects than other drugs although it increases the risk of cardiovascular disease. The investigators, most of whom had financial ties to Merck, explained the difference in cardiovascular disease risks as due to the protective effects of the other drugs. However, the VIGOR study did not include all of the cardiovascular risk data collected by the researchers. If it had, it would have shown that Voixx patients had five times the risk of having a heart attack or stroke as compared to patients taking other medications. In 2002, the FDA notified Merck that it had misrepresented Vioxx's safety profile and required the company to include a black-box warning on the drug label. In 2002, another study of Vioxx was stopped early to protect patients receiving the drug from cardiovascular risks. In 2004, Merck withdrew Vioxx from the market due to safety and liability concerns. Thousands patients who had a heart attack or stroke while taking Vioxx have sued the company (Shamoo and Resnik 2015).

The same year that Merck withdrew Vioxx from the market, a systematic review found that several selective serotonin reuptake inhibitors (SSRIs), including Paxil (paroxetine), Zoloft (sertraline), and Prozac (fluoxetine) increase the risks of suicide when prescribed to children and adolescents. Previous published studies had not shown that these drugs increase the risk of suicide in children or adolescents. However, the systematic review included data that had been reported to the

Committee on Safety in Medicines (a U.K. agency similar to the FDA) but had not been previously published. Parents and psychiatrists were understandably furious when they found out that companies had suppressed this data, and New York Attorney General Eliot Spitzer sued the manufacturer of Paxil, Glaxo Smith Klein, for fraud (Shamoo and Resnik 2015).

A fifth explanation of the funding effect is that financial interests may exert subconscious influences on researchers' judgment which bias the results (Resnik and Elliott 2013). Scientific research involves many different decisions that require the exercise of judgment, such as choosing the study design, sample size, interventions, procedures, measurements, and statistical methods. For many of these choices, there may be more than one option that researchers would regard as legitimate. Scientists who have financial interests related to a study research may be unaware that they are making choices that tend to bias the study in a particular direction (Resnik 2007a). Studies have shown that financial interests can exert powerful, subconscious influences over human behavior. Even small gifts, such as pens and free lunches, can influence our decision-making at subconscious level (Katz et al. 2003).

COIs raise ethical concerns not only because they can increase the risk of bias but also because they may influence interactions between investigators and subjects during recruitment and consent. An investigator with a COI may be strongly motivated to recruit subjects for a study so he or she can generate results. The investigator may overemphasize the benefits of the study and downplay its risks to encourage an individual to participate. Commentators on the Gelsinger case were concerned that that PI of the study, James Wilson, may have failed to fully inform Gelsinger of the risks of the research to encourage him to enroll (Resnik 2007a). Even government funded investigators may have strong incentives to recruit participants to generate results and maintain research support (Resnik 2007a).

A third reason why COIs raise ethical concerns is that they may cause harm to human subjects or increase the risks of harm. For example, if Gelsinger had received more information about the risks of Wilson's gene therapy study, he might not have enrolled and could be alive today. In addition to the Gelsinger tragedy, another case demonstrated how financial interests may increase risks to human subjects. In the Olivieri case (discussed above) patients could have suffered serious harm if she had succumbed to pressure from Apotex to suppress safety data. Investigators with less courage and integrity than Olivieri may allow pressures from corporate sponsors or their own financial interests to influence decisions related to the safety of patients in clinical trials (Krimsky 2003).

A fourth reason why COIs raise ethical concerns is that they may compromise institutional oversight of research. For example, an IRB member with a conflict of interest related to a study may be predisposed to approve the study and not criticize it. Although federal research regulations require that IRB members not have any COIs related to the research they are reviewing, they do not define conflicts of interest (45 CFR 46.107e). Additionally, university leaders may place pressure on the IRB to approve a study that is expected to generate significant income for the institution via contracts or grants. Since IRB members often have relationships with

other investigators or administrators at an institution, it can be difficult avoid or manage COIs in the review of research with human subjects (Shamoo 1999c).

Finally, COIs raise ethical concerns because they may undermine trust in research, especially when they are not fully disclosed (DeAngelis 2000; Institute of Medicine 2009). Human subjects, communities, other investigators, and members of public may be concerned the COIs may influence judgment, decision-making, and behavior and lead to violations of professional, ethical, or legal standards. As noted in Chap. 2, the failure to adequately disclose the investigator's and the institution's financial interests in the Gelsinger incident was a major ethical concern in this tragedy, which adversely impacted trust in gene therapy research and the University of Pennsylvania. When research subjects or members of the public discover that a COI has not been fully disclosed, they may believe that investigators or institutions are trying to deceive them (Shamoo and Resnik 2015). For example, when Moore discovered that his physician had not told him that he was commercializing a cell line developed from his leftover tissue, he felt manipulated and deceived (see discussion in Chap. 2). COIs may undermine trust even when there is no evidence that they have impacted judgment, decision-making, or behavior because members of the public and other outside observers may perceive that they have biased research (Resnik 2007a).

Before Jesse Gelsinger's death in 1999, several other incidents highlighted how COIs can undermine the integrity of research and the public's trust. In the late 1980s, a U.S. congressional committee on government operations began investigating cases of research misconduct and conflict of interest in biomedical science (United States Congress 1990). One of these involved research on Retin A, a cream containing a vitamin A derivative (trans-retinoic acid) manufactured by Johnson and Johnson. The FDA had approved Retin A in 1971 for treating acne. In 1988, the *Journal of the American Medical Association* published a study claiming that Retin A is effective at treating photo-aged (e.g. wrinkled) skin (Weiss et al. 1988). An accompanying editorial touted the benefits of the medication for reversing the effects of aging on the skin (Gilchrest 1988). Shortly after the study was published, several television newscasts covered the story, and Johnson and Johnson's sales of the product skyrocketed (United States Congress 1990). Several of the authors of the study began plugging the compound at national conferences and in television and radio interviews. In 1989, an exposé published in *Money Magazine* revealed that several of the authors of the study and the author of the editorial had financial interests related to the research that had not been disclosed in print. One of the authors of the study, John Vorhees, had received several hundred thousand dollars in research support from Johnson and Johnson, and compensation for consulting and speaking (i.e. honoraria). The author of the editorial, Barbara Gilchrest, had received honoraria from Johnson and Johnson and her department had received several hundred dollars in research support. The magazine article also found that the authors had used lighting techniques to make the cream appear to be more effective than it actually was and that they had not used double-blinding, as they had claimed in the article (United States Congress 1990).

Two other noteworthy cases involved investigators profiting from sales of stock related to their research. In 1985, Scheffer Tseng published an article showing that an ointment containing Vitamin A is effective at treating dry eyes but he did not disclose that the FDA had granted him exclusive rights to market the product or that he held 530,000 shares in Spectra, a drug company which was planning to purchase those rights for $310,000. The price of Spectra's stock soared after the paper appeared in print and Tseng sold his shares. Subsequent research showed the ointment was not as safe or effective as Tseng had claimed (Resnik 2007a). In 1997, Michael Macknin published a study in the *Annals of Internal* Medicine showing that zinc lozenges are effective at treating the common cold. Macknin had disclosed to the editors of the journal that he owned 9000 shares in Quigley Corporation, the manufacturer of the lozenges, but the journal did not share this information with the readers. Shortly after the paper appeared in print, Macknin made a $145,000 profit from selling his stock. Subsequent studies published by Macknin and other researchers have shown that the zinc lozenges are no more effective than placebos at treating the common cold (Resnik 2007a).

An incident involving the NIH's intramural program raised concerns about the integrity of government scientists. In 2003, a series of articles published in the *Los Angeles Times* reported numerous violations of the NIH's rules concerning outside activities for intramural researchers and some lucrative consulting arrangements with private companies that apparently did not violate existing rules. Two Congressional committees began investigating these allegations and NIH Director Elias Zerhouni appointed a panel to examine the matter and recommend changes in the organization's ethics rules (Kaiser 2004). To restore Congress' and the public's trust in the integrity of NIH research, the organization adopted some of the world's strictest COI policies. The rules prohibit all NIH researchers from engaging in paid consulting for pharmaceutical and biotechnology companies and other substantially affected organizations (SAOs). The rules also prohibit NIH leaders from owning any stock in SAOs and place limitations on the amount of stock that other employees may own in SOAs (Resnik 2005b).

10.7 Data Suppression

As mentioned in Chap. 6, the sharing of data, methods, materials, and results is essential to the progress of science. In Chap. 6, we considered ethical dilemmas involving conflicts between openness and transparency and protection of privacy and confidentiality in research. As noted above, private companies often have strong financial reasons not to share or publish data. Companies are not legally required to publish their studies and usually treat them as trade secrets. Private companies may suppress data not only promote their products but also to their intellectual property rights. To obtain a patent on an invention, the new product or process must not have been previously disclosed in the scientific or technical literature or prior art (Miller and Davis 2011). Since publication of research related to a new invention can

invalidate the patent, a scientist or research sponsor may wait to publish or share data related to a new invention until they have obtained a patent. Also, if a scientist shares data or ideas related to a patentable invention with other researchers, his or her invention could be stolen (Resnik 2003a, b, c).

The issue of whether data suppression constitutes fraud or research misconduct is complex. Data suppression is ethically problematic because it is highly deceptive and could be construed as a data falsification, which the U.S. government defines as "manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record (Office of Science and Technology Policy 2000: 76262." In some cases, it may be appropriate to exclude data outliers from the analysis if they result from experimental or human error or are more than two standard deviations from the mean (Shamoo and Resnik 2015). To avoid deceiving scientists or the public about study outcomes, investigators should discuss data exclusions in their published research. To adhere to principles of honesty and transparency in research, an investigator who excludes data should explain why certain data points were not included and analyze the data with and without the outliers to show that removing these data points clarifies a statistical relationship among variables but does not impact the overall results (Shamoo and Resnik 2015). However, excluding data without providing a sound scientific justification, as may have occurred in the VIGOR study, may constitute data falsification (Shamoo and Resnik 2015). Not publishing all of the data from different studies is different from excluding data from a particular study because the data are from different datasets and do not necessarily address the same hypothesis or research question. Moreover, there may be some good scientific reasons, such as poor experimental design or inadequate statistical power, for not publishing data from a particular study. Selective publication of studies may constitute a pattern of deceptive even if it is not data falsification (Michaels 2008).

In the early 2000s, many biomedical journals began requiring registration as a condition of publishing the results of a clinical trial in an effort to minimize data suppression (Dickersin and Rennie 2003, 2012). Scientific journals that follow guidelines from the International Committee of Medical Journal Editors (ICMJE) also require clinical trial registration (Laine et al. 2007). In 2007, the U.S. Congress passed a law requiring sponsors or designated investigators to register clinical trials of FDA-regulated drugs, biologics, and medical devices, other than Phase I studies (ClinicalTrials.gov 2017). Clinical trial registration involves posting some basic information about a study on a public website, including:

- The title
- Goals, objective, and hypotheses
- Design, methods, procedures, interventions, drugs
- Population, inclusion and exclusion criteria
- Sponsor(s), investigator(s), institution(s)
- Contact information
- Outcomes and related publications

The world's largest clinical trial registration website is ClinicalTrials.gov, which contains records from over 200,000 studies conducted in 193 countries (ClinicalTrials.gov 2017).

Clinical trial registration can help counteract data suppression, but it cannot prevent it. Although sponsors are required to publish trial outcomes and related publications, they are not required to publish data. Thus, a sponsor could publish the results of a study but not all of the data. However, since there would be public record of the study, interested scientists could ask the investigator or sponsor for access to the data.

Another way of minimizing data suppression is for universities to negotiate contacts with corporate sponsors that do not allow them to unreasonably delay or block publication of research. Boots was able to block the publication of Dong's study because it had signed a contract with the University of San Francisco giving it the right to review and approve publications (Resnik 2007a).

10.8 Dealing with Conflicts of Interest in Research

There are several strategies for dealing with conflicts of interest in research. The most basic one is to disclose COIs to interested parties, such as institutions, IRBs, research participants, journals, granting agencies, etc. (Institute of Medicine 2009; Shamoo and Resnik 2015). Disclosure embodies the virtues of honesty, openness, and transparency and allows interested parties to decide how to respond to the COI. Readers of journals articles may use COI disclosures to assess the credibility of the research (Resnik and Elliott 2013). A scientist who learns that the authors of a paper have significant financial relationships to a company that sponsored their research may decide to give the paper additional scrutiny to ascertain the validity of the data, methods, and approach. Human research subjects may consider COI disclosure relevant to their decision to enroll in a study (Resnik 2004). Jesse Gelsinger might not have participated in the study that led to his death if he had known the extent of the investigator's and university's financial COIs. Studies have found that most research participants or potential participants would like to receive information concerning financial interests and sources of funding related to the research (Kim et al. 2004; Grady et al. 2006; Coors et al. 2015).

Disclosure can also promote trust by assuring interested parties that significant interests are out in the open. Failing to disclose COIs can destroy trust, since parties that discover undisclosed interests may feel that the person with the COI has been trying to deceive them (Shamoo and Resnik 2015). While some have argued that disclosing COIs to human subjects may make them suspicious of investigators' motivations and undermine their trust in research (Thompson 1993), studies indicate that disclosure can have the opposite effect if done properly (Levinson et al. 2005; Coors et al. 2015). COIs disclosures should be expressed in non-technical language understandable to the subjects (Resnik 2004).

Granting agencies, such as the NIH and NSF, require researchers to disclose significant financial interests to the agency and their institution. The NIH, for example, requires funded extramural investigators or those seeking funding to disclose financial interests greater than $5000 to the agency and institution (Department of Health and Human Services 2011). The NIH and NSF both require institutions to establish committees to receive and manage COI disclosures (Shamoo and Resnik 2015). As noted above, the NIH also requires intramural researchers to disclose COIs and has oversight mechanisms for managing them. Most scientific journals also require authors to disclose financial or other interests related to submitted manuscripts (Cooper et al. 2006; Ancker and Flanagin 2007). IRBs also require investigators to disclose COIs to the committee and to human subjects (Shamoo 1999a; Shamoo and Resnik 2015).

While disclosure is a key strategy for dealing for dealing with COIs, it may not be sufficient to promote integrity and trustworthiness in many cases (Elliott 2008). Strategies that go beyond mere disclosure include avoidance and management (Shamoo and Resnik 2015). Avoidance involves taking steps to prevent the conflict from occurring, such as prohibiting or restructuring the situation that gives rise to the conflict. For example, the NIH and NSF prohibit individuals from reviewing research proposals from current or former (within the last 3 years) students, collaborators, or advisors (Shamoo and Resnik 2015). As mentioned above, the federal regulations forbid IRB members reviewing studies in which they have COIs. IRBs may allow a member with a COI to share information about the study with the committee but prohibit him or her from taking part in discussion or voting (Wolf and Zandecki 2007). Journal editors may ask peer reviewers not to evaluate manuscripts in which they have COIs (Shamoo and Resnik 2015).

Managing the conflict of interest may be the best option when avoidance is not feasible or it likely to have adverse consequences for science or society. For example, suppose that an investigator has patented a tool to be used in robotic surgery and she is planning to conduct a clinical trial of the device at an academic medical center. The investigator has also formed a startup company to develop, test, manufacture, and market the device. She also owns stock in the company. The investigator transferred the patent to the institution but will receive a share of royalties from it. The startup company will license the device from the institution. The institution also owns stock in the company. In this situation, there are numerous individual and institutional COIs that could affect the integrity and trustworthiness of the research. The COI committee reviewing this situation could mandate that the investigator and institution avoid the conflict by requiring the investigator to conduct the clinical trial at another institution or by requiring the investigator and institution to sell their stock in the company. However, this proposal could undermine product development and research. The investigator might be the best person to conduct and manage the study, and moving the study to another institution might compromise the quality of the research. If the investigator and institution sell their stock in the company, the company may suffer significant losses and go bankrupt. The best way to handle this situation might be to allow the study to take place on campus but require additional oversight of the research to ensure that human subjects are protected, that the

research is well-designed and properly implemented, and that data and results are published in a timely fashion (Shamoo and Resnik 2015).

Institutional COIs can be difficult to manage because there may not be an individual or committee within the organization with the authority or expertise to make fair and unbiased decisions concerning the institution's financial other interests (Resnik and Shamoo 2002). The Board of Trustees or similar body is responsible for ensuring that the institution achieves its academic, social, and economic goals and complies with ethical and professional standards. The Board could establish a committee to review and oversee COIs pertaining to the institution and its leaders. Other steps that institutions can take to manage their own COIs include separating research oversight from financial decision-making. For example, IRBs and compliance officers should be able to make decisions which are not influenced by the interests of the institution or its leaders. Institutions can also create foundations to hold institutional investments and intellectual property rights (Moses and Martin 2001).

To decide whether avoidance or management is the best way to handle a COI, one should consider the following factors (Institute of Medicine 2009; Shamoo and Resnik 2015):

- The strength of the conflict: how likely is it that the conflict will lead to bias, noncompliance, or other ethical or legal problems in research? How much money is at stake? What types of relationships, financial or otherwise, are involved?
- The difficulty of managing the conflict: does the institution have the resources to manage the conflict? Can the institution create special committees or other mechanisms to manage the conflict?
- The consequences of avoiding the conflict: what are the likely consequences of avoiding the conflict for human subjects, the investigator, institution, science, and society? Will avoiding the conflict prevent important research or product development from taking place? Will not avoiding the conflict undermine public trust?

Some scholars have proposed more radical ways addressing relationships between private companies and academic institutions. James Robert Brown (2000, 2002) has argued that the best way to minimize bias, corruption, secrecy, and other ethical problems related to financial interests in research is to sever the relationship between academic institutions and private corporations: Academic research should be funded by government grants, not private money. Brown also argues that biomedical patenting should cease so that investigators will share data more freely and drugs, biologics, other medical products and technologies will be accessible to public at low cost. Brown's solution to the problem of financial interests is to socialize academic research.

Brown's proposal is unrealistic and counterproductive. First, as noted earlier, private industry supports about 65% of R & D and governments are not likely to have the funds pay for research at current levels if one follows Brown's proposal. Brown's proposal would radically reduce the amount of research conducted on academic campuses and increased the amount conducted in private laboratories or corporate facilities. Since companies protect research under trade secrecy laws, shifting

research from academic campuses to private venues is not likely to increase openness, data sharing, or publication in science. Indeed, it would probably have the opposite effect. Moreover, purging private research funding from academic institutions is not likely to eliminate conflicts of interest, bias, or other problems, since ethically vexing situations can still arise when scientists compete for government funds (Resnik 2007a).

Second, foregoing biomedical patenting would have many adverse consequences for the development of drugs, biologics, medical devices, and other biotechnological inventions. Since the 1700s, the overarching rationale for the patent law has been to stimulate science and the practical arts (Resnik 2003b; Miller and Davis 2011). Prior to the advent of the patent system, scientists and companies relied on secrecy to protect their intellectual property. Governments started granting patents to encourage inventors to share their trade secrets with the public. In exchange for this disclosure, government allowed inventors to monopolize their work for a limited time. Under U.S. law, a patent grants the patent owner the right to exclude others from using, making, or commercializing his or her invention for 20 years from the date of the application (Miller and Davis 2011). The patent holder must submit an application to the patent office describing the invention and how to make and use it. Once the patent is awarded, the application becomes public (Miller and Davis 2011). Patenting provides economic incentives not only for inventors but also for investors. Private companies invest in R & D in order to profit from patented products or methods. Indeed, pharmaceutical companies derive most of the profits from new drugs when they are still under patent. While patented drugs are more expensive than drugs not protected by patents, once a patent expires prices drop precipitously, since other companies can manufacture and sell the drug, which introduces competition to the market (Resnik 2003a, b, c). Although patenting encourages secrecy while scientists are working on patentable research, publication and data sharing can take place when the patent is awarded. Overall, the benefits of patenting for biomedical science, biomedicine, and society outweigh the harms (Resnik 2003a, b, c).

Third, academic researchers and institutions benefit from collaborations with industry. In addition to receiving money to support research, academic scientists and institutions also benefit from exchanging information, knowledge, and ideas with their colleagues in industry (Resnik 2007a; Shamoo and Resnik 2015). They have the opportunity to work with companies who are developing cutting-edge products, methods, and technologies. Students can benefit from learning about real-world problems, internships with private companies, and employment opportunities in the private sector after graduation. Society can also benefit from collaborations between academic and industry that lead to the development of useful products, services, and technologies.

Others have made more modest proposals for dealing with relationships between academic institutions and private companies (Moses and Martin 2001; Morin et al. 2002; Krimsky 2003; Resnik 2007a; DeAngelis and Fontanarosa 2008; Angell 2008). Some of these, such as clinical trial registration, conflict of interest management, and review of contracts with companies to allow for publication, were discussed earlier. Others include:

- Increasing government sponsorship of clinical research to provide a source of data independent from industry. For example, the government could sponsor studies designed to compare different treatments available on the market so physicians and patients will have information concerning the comparative benefits, risks, and costs of these treatments (Resnik 2007a).
- Strengthening authorship criteria used by journals to clearly prohibit ghost authorship of scientific papers (DeAngelis and Fontanarosa 2008, see discussion Chap. 2).
- Empowering journals to deal with undisclosed COIs. A journal which discovers that an author has failed to disclose a significant financial or other interest related to his or her research could prohibit the author from publishing in the journal for a period of time (Goozner 2004).
- Coordinating COI management at institutions. For example, faculty COI committees should provide IRBs with disclosure information. Likewise, IRBs could share information relevant to COI assessment with faculty committees.

10.9 Conclusion

In this chapter I have examined several research integrity issues which have a direct bearing on protection of human subjects. These problems are important to address because they can increase risks to subjects, reduce benefits, undermine informed consent, compromise data, and damage the trustworthiness of research. Because investigators are not perfect, deliberate misbehavior, subconscious bias, and honest mistakes are likely to occur in research involving human subjects. Academic institutions, public and private research sponsors, and scientific journals should develop policies, procedures, administrative structures, and educational programs to prevent these problems and deal with them effectively and fairly when they occur. Leadership, mentoring, auditing, and accreditation can also play a key role in promoting research integrity. In the next chapter, I will move beyond issues impacting individuals and institutions and explore ethical and policy questions related to oversight of research with human subjects at the national level.

Chapter 11
Regulatory Reform

In Chaps. 5, 6, 7, 8, 9, and 10 I examined various ethical and policy issues pertaining to research with human subjects through the lens of five principles—respect for autonomy and dignity, non-maleficence, beneficence, justice, and trust. Along the way, I also discussed how federal regulations, agency guidance, and professional codes apply to those issues and mentioned recent changes to the Common Rule. In this chapter I will turn my focus to critiques of the current oversight system and recent changes to the regulations. At the end of Chap. 2, I raised the issue protectionism and suggested the determining the right level of protection for human subjects requires one to balance conflicting values, i.e. protection of human welfare and rights vs. the advancement of scientific knowledge. In this chapter, I will consider how regulatory reform efforts achieve this balance.

11.1 Institutional Review Boards: A Time for Reform

During the 1990s, criticisms of the federal regulations and the IRB system emerged and have continued to the present day. In 1998, the Office of General Counsel for the DHHS issued a report "Institutional Review Boards: A Time for Reform," which identified a number of problems with the IRB system (Department of Health and Human Services 1998). According to the report, changes in the research environment since the 1970s, such as increases in the quantity and complexity of studies, placed pressures on IRBs that they were not prepared to deal with. The report said that many IRBs review too many studies, do not devote sufficient attention to continuing review; have conflicts of interest that compromise the integrity of review; are overburdened and understaffed; and lack sufficient education, experience, and institutional support to perform review competently. The report made several recommendations for reforming the system, including increasing IRB staffing and institutional support, and requiring more education and training for IRB members.

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The report also recommended that IRBs should focus more on substantive rather than procedural issues, and that they should regularly evaluate their performance (Department of Health and Human Services 1998). Federal agencies responded to the report by mandating more education and training for IRB members and encouraging institutions to provide more support for IRBs.

In 1999, the same year that Jesse Gelsinger died in a gene therapy experiment, the Office of Protection from Research Risks (OPRR), which is now known as the Human Research Protections (OHRP), temporarily halted all human studies at Duke University Medical Center (DUMC) after an audit found that DUMC had inadequate procedures to protect the safety of clinical trial participants, poor-recording keeping, and inadequate continuing review. The DUMC shutdown sent shockwaves through the research community, because Duke University was (and still is) one of the most prestigious and well-funded academic institutions in the U.S., garnering hundreds of millions of dollars per year in federal research support. OPRR also halted research at seven other institutions that year (Institute of Medicine 2001).

In 2001, an Institute of Medicine report recommended accreditation as a mechanism for improving the quality of and effectiveness of ethical oversight of research with human subjects (Institute of Medicine 2001). That same year the Association for the Accreditation of Human Research Protection Programs (AAHRPP) began accrediting research institutions, hospitals, and IRBs that oversee research with human subjects (Smith 2008). AAHRPP has developed standards for human research protection programs (HRPPs) which it uses to make accreditation decisions. The standards address institutional support for the HRPP, including staffing and funding; the organization of the HRPP, including potential conflicts of interest; education and training for IRB members, IRB staff, and researchers; and SOPs (Association for the Accreditation of Human Research Protection Programs 2012a). The accreditation process includes a site visit in which AAHRPP representatives examine IRB records and interview IRB members, staff, researchers, and institutional leaders. AAHRPP has accredited over 200 organizations in 11 countries, including 65% of the medical schools and 60% of the research-intensive universities in the U.S. (Association for the Accreditation of Human Research Protection Programs 2012b).

From 1998 to 2001, President Clinton's National Bioethics Advisory Commission issued several reports dealing with ethical and regulatory issues in human subjects research, addressing such issues as: research involving disabled or ill human subjects; research with human biological samples; IRB accreditation, education, and oversight; human stem cell research; and clinical trials in developing nations (National Bioethics Advisory Commission 1998, 1999, 2001a, b).

Several themes have emerged from these different critiques of the regulations and IRB system:

11.2 Risk-Based Review

For many years, social and behavioral researchers have maintained that their studies do not need full board review because they are low-risk. IRBs should pay less attention to social/behavioral research and focus their attention on high-risk biomedical research (Gunsalus et al. 2006, Schrag 2010). Others have asserted that some types of data collection activities, such as student projects, oral history, QA/QI, and public health studies do not need to be reviewed by an IRB because they are not human participant research or they are subject to oversight from other entities (Kass et al. 2013). Finally, some have argued that continuing review of approved studies is not necessary when investigators have stopped enrolling new human subjects and are analyzing data or conducting routine follow-up activities (Emanuel and Menikoff 2011).

The gist of these arguments is that the regulations are overprotective because they provide more safeguards for human subjects in low-risk research than are necessary. IRB review should be proportional to risk: high-risk studies should have full board review, low-risk studies should have expedited review, and some studies should have no review (Rhodes et al. 2011). As noted in Chap. 2, the federal research regulations already include a framework for proportioning review on the basis of risk. Studies which are classified as exempt or not human subjects research do not need IRB review, and those which are minimal risk can receive expedited review. However, critics have argued for expanding the exemptions. The revisions to the Common Rule (discussed below) address this concern.

Risk-based review makes a great deal of sense, since it uses the IRB's resources effectively. If an IRB spends too much of its time and effort focusing on low-risk studies, it may fail to adequately review riskier studies that warrant more careful scrutiny (Rhodes et al. 2011; Emanuel and Menikoff 2011). The only potential problem I see with proportioning review to the degree of risk is that sometimes IRB chairs or designees may incorrectly determine that a study is minimal risk, exempt from review, or not human subjects research. When this occurs, the study may fail to receive adequate review and oversight. Allowing investigators to make these determinations could be especially problematic, since they may not understand how to apply the different categories and they are likely to have a strong interest in avoiding IRB review. To prevent these problems, institutions should develop procedures to oversee these determinations and educate decision-makers on applying the categories correctly.

11.3 IRB Mission Creep

Commentators have argued that IRBs have taken on oversight responsibilities that go beyond their original mission (Gunsalus et al. 2006). Some of these include: reviewing studies that are not human subjects research (see discussion above);

dealing with HIPAA requirements (see discussion in Chap. 6) and scientific issues (see discussion in Chap. 7); reviewing radiation safety and biosafety reports; and handling investigator COI disclosures. IRBs have acquired these responsibilities, in part, because they are often the final body that must approve a study before it can begin and they want to ensure that all other institutional requirements have been met. Although many institutions have committees to deal with COI disclosures, radiation safety, and scientific review, IRBs often find themselves addressing issues that are not strictly within their purview.

11.4 IRB Conflict of Interest

As noted in Chap. 10, IRBs may themselves have COIs which can be difficult to manage. COIs may occur when IRB members have interests related to studies they are reviewing or when the board faces pressures from within the institution (Shamoo 1999a).

11.5 Difficulties with Measuring IRB Performance

Several commentators have noted that there are currently no validated methods for measuring IRB performance (Emanuel et al. 2004; Abbott and Grady 2011, Grady 2015; Nicholls et al. 2015). This criticism is not completely accurate, because the IRB Researcher Assessment Tool (IRB-RAT) is a validated method for measuring performance used by many institutions (Hall et al. 2015). However, the IRB-RAT has not been widely adopted, in part, because it is a self-assessment tool that does not provide an objective measure of important variables related to IRB performance, such as costs, efficiency, expertise, knowledge of regulations and guidelines, consistent and competent application of regulations, adverse outcomes for participants (including injuries and complaints), and relationships with investigators (Sugarman et al. 2005; Abbott and Grady 2011; Resnik 2015d).

11.6 Centralized IRB Review

Numerous critics have argued that multiple-IRB review of the same study is time-consuming, inefficient, costly, and often unnecessary (Millum and Menikoff 2010; Silberman and Kahn 2011; Ervin et al. 2015). In a large multisite clinical trial a dozen or more IRBs may need to review the same study. An investigator may need to go back and forth between different IRBs to address their stipulations, which can delay final approval by many months. For an extreme example of inefficiency, consider Petersen et al.'s (2012) study of health services at Veteran's Administration

health centers, which required 115 separate submissions to 17 IRBs and cost $170,000 in staff salaries. It took 17 months for the investigators to secure final approval of their study at all of the participating centers (Petersen et al. 2012). Once the investigator obtains approval from all of the IRBs, he or she will still need to correspond with them concerning amendments, problem reports, continuing reviews, and so on, which increases the amount of time and effort the investigator or his or her staff must devote to the study. From the IRB perspective, multiple-review is wasteful because an IRB may need to spend its time reviewing a proposal that has already been approved by another board (Silberman and Kahn 2011; Resnik 2012e).

Another key argument for centralizing IRB review is to promote consistency, since different IRBs may sometimes make divergent decisions concerning the same study (Resnik 2012e, 2015c). Inconsistency creates practical problems with obtaining final approval from all collaborating institutions and increases the investigator's burdens and frustrations as he or she tries to negotiate between different IRB requirements. Inconsistency may be ethical problem if it involves unequal protection of human research subjects (Resnik 2015c). For example, McWilliams et al. (2003) found that 31 IRBs at different research sites categorized the same genetic epidemiology study differently: 7 (23%) classified it as minimal risk and gave it expedited review and 24 (77%) classified it as more than minimal risk and gave it full board review. 16 IRBs (52%) required only one consent form, while 15 (48%) required two or more. 21 IRBs (68%) required an assent form for children while 10 (32%) did not (McWilliams et al. 2003). As argued in Chap. 5, obtaining the child's assent can be an important part of ethical enrollment in pediatric research. If an IRB does not require a study that recruits adults and children to include an assent form, it may not be providing adequate protections for pediatric research subjects.

There are several ways of centralizing IRB review. First, collaborating institutions could negotiate a contract (known as a reliance agreement) in which one institution agrees to provide IRB review and oversight for the other institution. The relied-upon institution becomes the IRB of record for the study and reviews the initial proposal, amendments, renewals, problem reports, and other actions. A reliance agreement might cover a single study, multiple studies, or an institution's entire human research portfolio (Resnik 2012e). Second, collaborating institutions in a multisite clinical trial could agree to use a central IRB to review the study. The central IRB could be an independent, private IRB, or an IRB associated with a funding organization. For example, the National Cancer Institute (NCI) supports several central IRBs that review and oversee NCI-funded multisite oncology studies (Resnik 2012e). Third, institutions could use an IRB to review research within a geographic region, such as a territory or state. For example, the Indian Health Service supports an IRB that reviews research conducted in several different Native American tribes (Resnik 2012e).

There are some arguments against centralizing IRB review, however. First, one might argue that local IRBs can provide crucial input concerning the context of the research, such as information pertaining to cultural traditions, community interests and values, language barriers, and socioeconomic conditions (Resnik 2012e; Solomon 2016; Nicholls et al. 2017; Klitzman et al. 2017). Centralizing

IRB review and oversight might fail to take the local context into account (Wisconsin IRB Consortium 2011; Resnik 2012e). For example, a local IRB could provide important information related to methods used for recruitment or consent and community concerns about the use of biological samples or data. Although commonsense and anecdotal evidence suggest that local review can provide valuable input concerning the context of the research, the evidence obtained so far does not support this hypothesis (Department of Homeland Security et al. 2015). However, the studies which have been published thus far have not systematically investigated how local IRBs contribute to the review of multisite research (Resnik 2012e). Additionally, there are other ways of obtaining local input without using a local IRB, such as consulting with community representatives or advisory boards concerning the implementation of a multisite study in a particular venue.

Second, one might argue that local review is important for holding investigators and institutions accountable to the local population and building the community's trust (Solomon 2016). Community members may be wary a study approved by an IRB located in a distant location with no representatives from their locality. They may also feel alienated from the study if they believe it does not address their interests or concerns. Community distrust of a non-local IRB could be especially acute when investigators from a developed nation are conducting research in a developing country, due to significant differences in values, culture, access to health care, wealth, and so on. Distrust could also occur when investigators from a distant region of the U.S. conduct research in a socioeconomically disadvantaged or culturally unique community. As we have stressed throughout this book, trust is an important commodity in research with human subjects, and processes and guidelines should seek to promote it.

Third, institutions may be concerned about legal liability related to centralized review, especially for risky studies involving novel drugs, biologics, devices, or procedures. Attorneys at local institutions may decide that the best way to minimize legal liability is to maintain local control of the research, without deferring to an outside IRB. Conversely, attorneys at relied-upon institutions might advise against assuming liability for risky research conducted at another site. If collaborating institutions are required to use a single IRB, they may avoid engaging in cooperative research activities to minimize their legal risks (Millum and Menikoff 2010; American Lung Association 2011; Ervin et al. 2015; Klitzman et al. 2017; Nicholls et al. 2017).

The revisions to the Common Rule (discussed below) include a mandate for a single IRB in multisite research and address some of the centralization issues discussed in this section.

11.7 Lack of Harmonization of Regulations

As we saw in Chap. 2, there are differences among federal agencies with respect to protecting research subjects. Although 17 agencies have adopted the Common Rule, there are still significant differences between this regulation and the FDA and EPA regulations. For example, the FDA includes special rules for waiving informed consent for emergency medical research, but the Common Rule does not include such provisions. The EPA regulations include special protections for children and pregnant and nursing women which go beyond the protections found in the Common Rule's protections for vulnerable subjects, i.e. Subparts B and D. The lack of harmonization among different agency rules could create confusion among investigators and IRBs as they attempt to apply the regulations to studies covered by conflicting requirements. For example, if the EPA and the NIH collaborate on a study involving children, investigators would need to decide how to resolve potential conflicts between EPA and NIH rules. Harmonization of federal regulations could improve the efficiency and consistency of human research review and oversight (Emanuel et al. 2004, Department of Health and Human Services and Food and Drug Administration 2011).

11.8 Gaps in the Regulations

The federal research regulations cover human subjects research funded by federal agencies or submitted to the FDA or EPA for regulatory decision-making. However, the regulations do not cover privately funded research that is not submitted to the FDA or EPA. For example, Facebook's study (discussed in Chap. 1) would not have been covered by any research regulations if it had not included collaborators from academic institutions. Other types of research not covered by the federal regulations include privately funded marketing studies, public opinion surveys, and non-FDA regulated consumer product testing. The Advisory Committee on the Human Radiation Experiments (1995) and the National Bioethics Advisory Commission (2001a) recommended that the federal government close these loopholes and develop a national system for oversight of human subjects research. Others have made similar recommendations (Shamoo 1999b, Shamoo and Schwartz 2008). Two U.S. states, California and Maryland, have developed their own statutes to regulate human research not covered by federal law. Closing the gaps in the existing regulations would help to ensure that common ethical standards apply to all human subjects, regardless of the source of funding or the purpose of the research. It could also help to promote the public's trust in the research enterprise by providing oversight for studies not covered by the current regulatory framework. However, extending the federal research regulations may be a difficult sell politically, because it would increase the government's regulatory reach and impose significant costs on businesses (Schneider 2015).

11.9 Problems with Informed Consent

Numerous commentators have observed that consent documents are often long, complex, replete with jargon, and difficult to read (Emanuel et al. 2004; Flory and Emanuel 2004). In spite of their length, consent documents may sometimes lack important information and may not explain to potential subjects why they should or should not participate in a study (Menikoff 2006). For example, consent documents may not provide human subjects with enough information concerning the use of their biological samples and data (National Bioethics Advisory Commission 1998; Cadigan et al. 2016) or the availability of treatment off-study (Resnik et al. 2008a, b). Consequently, human subjects may often fail to understand important information related to participation in research (Menikoff 2006). Commentators have also observed that IRBs often devote a considerable amount of time to making grammatical or wordsmithing changes to consent documents that do not significantly improve protection of human subjects (Klitzman 2015; Schneider 2015). The revisions to the Common Rule (discussed below) address some of these concerns.

11.10 Compensation for Injury

As mentioned in Chap. 6, the federal regulations do not require that institutions or sponsors compensate human subjects for research-related injuries even though numerous bioethics advisory commissions have recommended that the U.S. adopt a national policy for compensating human subjects for research related injuries (Pike 2012, 2014). Although many European, Asian, and African nations have such a policy, the U.S. does not (Pike 2014). In the absence of a national policy, institutions and sponsors have developed their own compensation programs (Resnik et al. 2014). While these programs can help address issues pertaining to compensation for injury, they do not guarantee uniform protections for research subjects.

11.11 Revisions to the Common Rule

In response to years mounting criticisms of the IRB system and the federal regulations, on July 26, 2011, the DHHS (via OHRP) and the FDA began the process of revising the regulations and published an Advance Notice of Proposed Rulemaking (ANPRM) in the Federal Register (Department of Health and Human Services and Food and Drug Administration 2011, Emanuel and Menikoff 2011). After holding several public meetings and responding to thousands of comments, the organizations released a Notice of Proposed Rulemaking (NPRM) on September 8, 2015 (Department of Homeland Security et al. 2015). The DHHS sponsored additional public meetings and reviewed more comments in response to the NPRM. As

mentioned earlier in this book, the Obama administration announced the Final Rule on January 19, 2017 (Department of Homeland Security et al. 2017). With the exception of the single IRB mandate (discussed below), the regulations become effective on January 19, 2018. The revisions apply only to new studies; studies approved under the old regulations are grandfathered in. The Trump administration may still seek to make additional changes in the regulations or delay their implementation. The stated goals of the revisions were to: (1) reduce regulatory burden and (2) enhance protections of human subjects (Department of Homeland Security et al. 2015, 2017). As we have noted throughout this book, these two goals often conflict, since policies that enhance protections for human subjects frequently increase regulatory burdens. Below is a summary of the most important changes with some commentary, some of which have been mentioned earlier in this book.

11.12 Expanding Exemptions

The revisions to the Common Rule reduce regulatory burden by expanding research exempted from IRB oversight. Under the old regulations, research on **previously** existing, de-identified human samples or data was exempt. The revisions eliminate the requirement that de-identified samples or data be previously existing, so that concurrent collection and sharing of samples or data can qualify as exempt (Department of Homeland Security et al. 2017 at 45 CFR 46.104d4). Research involving secondary use of identified examples or data is also exempt if the subjects have given broad consent to use and share their samples or data and the research includes appropriate safeguards[1] for protecting privacy and confidentiality, which can be reviewed on an expedited basis (45 CFR 46.104d8). Both of the changes in Final Rule make it much easier for researchers to acquire and share human biological samples and data and stand in sharp contrast to a proposal contained in the NPRM to define human biological samples as human subjects (Department of Homeland Security et al. 2015). If all human biological samples were treated as human subjects, then research involving such samples could not take place unless subjects had previously consented or an IRB had waived consent. This proposal was eliminated from the Final Rule after numerous investigators and research organizations complained that it would significantly hamper biomedical research involving human biological samples (Kaiser 2016, Nicholls et al. 2017).

The revisions also expand exemptions for social/behavioral research. Under the old regulations, research involving interviews or surveys was exempt only if data were recorded in a way that did not identify human subjects or public disclosure of the data would not place subjects at unreasonable risk of "criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation (45 CFR 104d2)." Since surveys and interviews often collect sensitive information with legal, financial, or reputational consequences, this

[1] OHRP will provide a list safeguards for protecting the confidentiality of human subjects data.

provision in the old regulations had the practical effect of making most survey or interview research that identifies human participants as non-exempt. Under the new regulations, this research is exempt as long as it includes appropriate safeguards to protect privacy and confidentiality (45 CFR 102d2).[2]

The revisions also include a new exemption category, benign behavioral interventions. To qualify for this exemption, the data must be recorded in a manner that does not identify human subjects; or, if it identifies human subjects, appropriate safeguards must be in place to protect privacy and confidentiality (45 CFR 46.104d3). The regulations clarify that benign behavioral interventions "are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects (45 CFR 46.104d3ii)." Benign behavioral interventions cannot include deception unless the subject prospectively agrees to it (see discussion in Chap. 5).

11.13 Defining Some Activities as Not Research

To limit IRB review, the revisions explicitly define some data collection activities as not research. These include: "Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected," "Public health surveillance activities," and "Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes," and "Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions (45 CFR 46.102l1-4)."

11.14 Limiting Continuing Review

The revisions to the Common Rule state that an IRB need not perform continuing review for research that is classified as minimal risk or research that is limited to data analysis or follow-up as part of routine clinical care, unless the IRB determines otherwise (45 CFR 46.109f1). Limiting continuing review is likely to significantly reduce administrative burdens on investigators and IRBs without negatively impacting the welfare of human subjects (Nicholls et al. 2017).

[2] The IRB chair can do a limited review of these safeguards to ensure that they adequately protect privacy and confidentiality (45 CFR 102d2).

11.15 Single IRB Mandate

The regulations require a single IRB for collaborative research located in the U.S. Since it may take some time for institutions to negotiate reliance agreements and make other arrangements for using a single IRB, this requirement does not become effective until January 20, 2020 (45 CFR 114). Exceptions to the single IRB mandate include research for which local law (including tribal law) requires more than one IRB, or research for which a federal department or agency determines that a single IRB is not appropriate, given the context of the research. It is worth noting that NIH adopted a single IRB requirement for its funded research in anticipation of the changes to the Common Rule. The NIH requirement, which becomes effective on January 25, 2018, is nearly identical to the Common Rule requirement (National Institutes of Health 2017). The NIH is developing criteria for determining when a single IRB is not appropriate.

11.16 Informed Consent Enhancements

The revisions to the Common Rule include numerous provisions intended to enhance informed consent. Some these added requirements include:

- "The prospective subject or the legally authorized representative must be provided with the information that a **reasonable person** [emphasis added] would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information (45 CFR 46.116a4)." (See Chap. 5 for discussion of the reasonable person standard for information disclosure.)
- "Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension…[Information] must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate (45 CFR46.116.5) (See Chap. 5 for discussion of understanding and comprehension of information.)
- "[For research involving identifiable biospecimens or private data, informed consent must include] (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed,

will not be used or distributed for future research studies (45 CFR 46.116b9)." (See Chap. 5 for discussion of consent related to sharing of biological samples or data.)

- "[Where appropriate, informed consent must include] A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit (45 CFR 46.116c7)." (See Chap. 5 for discussion of consent related to sharing of biological samples or data.)
- "[Where appropriate, informed consent must include] A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions (45 CFR 46.116c8)." (See Chap. 8 for discussion of sharing individualized research results with human subjects.)
- "For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen) (45 CFR 46.116c9)."

11.17 Abridged Consent Process for Research Involving Biological Samples

The revisions to the Common Rule describe an abridged process that investigators may use when the sole purpose of the study is collect identifiable biological specimens or private information. The process is an alternative to the consent requirements that govern research involving more than the collection of identifiable samples or private data (Hurley 2015). This process requires investigators to inform subjects (or their legally authorized representatives) about reasonably foreseeable risk; expected benefits; confidentiality protections; that participation is voluntary and that they may refuse to participate without penalty; whether biospecimens will be used for commercial profit; whether whole genome sequencing will be performed on biospecimens; general description of the types of research that may be conducted; description of the biospecimens or data that may be used in research; the types of institutions or researchers that biospecimens or data may be shared with; how long biospecimens or data may be stored, maintained, or shared; that subjects may not be informed of the specific details about whom specimens or data are shared with (unless they have consented otherwise); whether clinically relevant research results with shared with subjects; and whom to contact about the subject's rights and storage of biospecimens and data (45 CFR 46.116d). An IRB may not alter or waive informed consent requirements when the abridged consent process is used. An IRB also may not waive consent requirements if an individual explicitly refused to allow sharing of their samples or data (45 CFR 46.116e).

11.18 Additional Changes to Informed Consent Requirements

Some additional changes to the Common Rule's informed consent requirements include:

- An IRB can allow consent to be altered or waived for research involving the collection of identifiable biospecimens if the research is minimal risk and could not be carried out without the alteration or waiver, however this provision does not apply when the abridged consent process is used (45 CFR 46.116f).
- An IRB may allow an investigator to obtain identifiable biospecimens or private information without consent from the subject (or representative) for the purpose of screening, recruiting, or determining eligibility for a study (45 CFR 46.116g). This is consistent with allowable exceptions to the HIPAA Privacy Rule discussed in Chap. 6.
- IRB-approved informed consent documents for clinical trials sponsored by federal agencies or departments must be posted on a publicly available federal website (45 CFR 45.116h).
- An IRB may waive documentation of informed consent if the subjects or their representatives belong to a cultural group for which signing documents is not the norm and the research is minimal risk (45 CFR 117c1).

11.19 Conclusion

In this chapter, we have reviewed critiques of the human research regulations and described revisions to the Common Rule that were intended to address some of them. Regarding the issue of balancing protection for human subjects and the advancement of science, the revisions do a little bit of both. Expanding exemptions and limiting continuing review will undoubtedly help promote scientific research by reducing administrative burdens on investigators and IRBs (Nicholls et al. 2017). These changes may also enhance human subjects protections by allowing IRBs to devote more of their attention to high-risk studies. Changes to the consent requirements are likely enhance protections for human subjects by providing potential participants with more—and better—information about research (Nicholls et al. 2017). However, because these new requirements are subject to interpretation, they may increase administrative burdens because institutions may be unsure of how to apply them and may be wary of using an interpretation that may create liability for noncompliance with federal regulations (see discussion of SUPPORT in Chap. 1). To alleviate these concerns, OHRP and other federal agencies should move quickly to publish interpretative guidance for investigators, institutions, sponsors, and IRBs (Nicholls et al. 2017). The single IRB mandate for collaborative research is likely to reduce administrative burdens in the long run by eliminating redundant IRB review

but it may also create legal and practical problems in the short run as institutions negotiate reliance agreements and make arrangements for research review and oversight. This mandate could have a negative impact on human subjects protections if institutions fail to adequately address the local context of research during the review and oversight process (Nicholls et al. 2017; Klitzman et al. 2017).

It is also important to note what the changes to the Common Rule do not do. First, the changes do not close gaps in the federal regulations. Some types of studies, such as research conducted by private companies who are not planning to submit data to the FDA or EPA, will continue to escape federal regulatory oversight. Second, the changes do not address compensation for research-related injuries. As a result, some human subjects who are harmed in research may continue to have difficulty obtaining treatment or reimbursement for medical care at institutions which do not have a compensation for injury policy. Third, the changes do not completely harmonize the federal regulations because there are still substantial differences between the Common Rule and FDA and EPA regulations. Fourth, the regulations do not address the issue of measuring IRB performance.

It remains to be seen what impact, if any, these changes will have on trust in human subjects research. While some of the enhancements to the consent process could promote trust by providing human subjects with more information, the single IRB mandate has the potential to undermine subjects' and the local community's trust, because they may feel alienated from a remote IRB overseeing the research.

Despite some shortcomings, the revisions to the Common Rule are a significant achievement which should reduce administrative burdens and enhance protections for human subjects. There is still much more work to be done however, since investigators, IRBs, and institutions must now carefully study the changes and learn how to implement them appropriately.

Chapter 12
Conclusion

In this book I have covered a broad array of issues pertaining to the ethics and regulation of research involving human subjects, ranging from theoretical and historical matters to practical and policy dilemmas. In the first chapter, I observed that moral predicaments involving research with human subjects often boil down to a conflict between protecting individual rights and welfare and promoting scientific research that benefits the public. I argued that while most people agree that both values are important, ethical disagreements can arise with respect to priority-setting. I suggested that a philosophical framework that emphasizes promoting trust can help us set priorities when values conflict. I set the stage for my trust-based approach by reviewing the history of research with human subjects in Chap. 2 and examining influential moral theories in Chap. 3. In Chap. 4, I reflected on the nature and importance of trust and discussed some strategies for promoting trust among the various stakeholders in involved in research, i.e. subjects, investigators, institutions, communities, sponsors, IRBs, and the general public. I argued that we can apply four widely recognized moral principles, respect for dignity and autonomy, nonmaleficence, beneficence, and justice to practical and policy questions involving research with human subjects and that we can appeal to the goal of promoting trust to adjudicate conflicts among the four principles. The trust principle compliments the other four principles but it is not a meta-rule that can resolve all conflicts. Difficult questions may still arise when trust conflicts with other principles, such as respect for dignity and autonomy or justice. Even so, the principle can play augment and fortify ethical decision-making in research with human subjects. In Chaps. 5, 6, 7, 8, 9, 10 and 11, I applied my decision-making framework to various topics in research with human subjects, including informed consent, privacy and confidentiality, risks, benefits, vulnerable subjects, research integrity, and regulatory reform.

Advocating for trust in research with human subjects is hardly a new idea. As I noted in Chap. 4, numerous national commissions, investigators, and bioethicists have emphasized the importance of trust in articles, books, and other writings. What is potentially novel about my approach is that I have gone further than most

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commentators in examining the conceptual foundations and practical applications of trust. I have argued that promoting trust should be a centerpiece of ethical research with human subjects on a par with other key ethical considerations. Rather than review all of the book's findings and recommendations I will mention a few that relate specifically to trust. While most of these findings and recommendations are also supported by other ethical principles, such as respect for dignity/autonomy, non-maleficence, and so on, my summary will focus on trust.

12.1 Trust and Consent

- Some strategies for promoting trust in research with human subjects include: informed consent; community engagement; community representation on IRBs; public engagement; development of regulations, guidelines, and standard operating procedures pertaining to research oversight and compliance; leadership; education in research ethics and compliance; disclosure and management of conflicts of interest; and compensation of subjects for research injuries.
- Consent presumes a certain degree of trust because subjects often rely on investigators to help them understand the information they receive. The principle of trust implies that investigators should take subject-specific and community or population-specific informational needs into account when obtaining consent.
- Patients' trust in their doctors can contribute to the therapeutic misconception by predisposing them to believe that studies they are participating in are designed solely to benefit them. Clinical investigators should help their patients overcome this misunderstanding while maintaining their trust. Patients with terminal or incurable illnesses may be especially susceptible to the therapeutic misconception, since they may be willing to try anything that will give them the hope of a cure
- Documentation of consent can promote trust by providing subjects with a written record of research procedures and methods, risks, benefits, confidentiality protections, and so on. Documentation may undermine trust when research is conducted in a community in which most people prefer oral communication and are suspicious of written documents. Investigators should use culturally appropriate methods for documenting consent.
- Informed consent processes involving people other than the research subjects (such as tribal leaders or spouses) should honor cultural traditions without violating the subject's autonomy or privacy.
- Conducting research on medical records or leftover biological samples without consent can undermine patient's trust in doctors and institutions. Upon admission, hospitals and clinics should give patients an opportunity to opt out of research involving their medical records or leftover biological samples, and their decision should be noted prominently in their medical record.

- Health care institutions should also inform patients if they are conducting QA/QI research to improve the quality of their care and they should inform the public about the result of their QA/QI efforts.
- Opt-out procedures are more likely to cause distrust than opt-in procedures, since subjects who discover that they are enrolled in research and claim that they were not aware of how to opt out may feel that they have been deceived or manipulated. Opt-out consent procedures should be used only when opt-in procedures are impractical and risks are minimal.
- Investigators who are collecting biological samples or data should offer subjects a variety of options concerning the use of samples/data, including: no sharing allowed; sharing allowed for research purposes; and sharing allowed only for specific types of research. The menu approach can build trust by honoring subjects' and communities' preferences concerning the use of samples and data.
- Since deception of research subjects may undermine trust in investigators or institutions, it is important for researchers and IRBs to take appropriate measures to minimize the damage caused by deception when it is part of the research methodology, such as informing subjects that they may be deceived.
- While many bioethicists are concerned that paying subjects too much money for their participation can lead to undue inducement, underpayment is likely to have more of negative impact on trust than overpayment, because subjects who are not paid enough money may feel that they are being exploited, underappreciated, or otherwise mistreated. Ensuring that subjects are adequately compensated is a way of recognizing the value of their contributions to research.

12.2 Trust and Confidentiality

- Protecting privacy and confidentiality is important for promoting trust. Breaches of confidentiality or privacy can seriously damage trust subjects' and community's trust in investigators and institutions, as well as the public's trust in the research enterprise.
- Informed consent documents and discussions should provide research subjects (or their representatives) with information about measures investigators will use to protect confidentiality, as well as circumstances in which they may be required by law to breach it.
- Investigators should use material transfer agreements (MTAs) and data use agreements (DUAs) when should genomic data and biological samples to protect confidentiality and promote trust. These agreements should spell out the conditions for using the data or samples, including the requirement that recipients will not share samples or data without permission or try to re-identify individuals.
- Investigators may breach confidentiality when a subject poses a serious threat of harm to himself or others, or to report suspected abuse/neglect or communicable diseases.

12.3 Trust and Risks

- Serious harms to human subjects can significantly undermine trust in investigators, institutions, sponsors, and the scientific enterprise, and proper management of risks is very important for promoting trust in research with human subjects.
- Because subjective perceptions of harm or risk can negatively impact trust, even studies which are classified as minimal risk may raise difficult ethical issues. Investigators and IRBs should take community perceptions of risk into account when applying the definition of minimal risk to research studies.
- Limits on risks that healthy volunteers are allowed to face in research can be justified to prevent catastrophic outcomes that can seriously undermine the public's trust in scientific research. For healthy volunteers enrolled in research, the risk of a serious adverse event should not be greater than 1% and the risk of death should not be greater than 0.065% (65/100,000).
- Enrolling subjects in placebo-controlled clinical trials when an effective therapy exists is controversial, in part, because the subjects who receive placebos face significant risks without compensating medical benefits. If we think of subjects in placebo-control groups as like healthy volunteers because they are not receiving medical benefits from participation, then the risks they face should similar to those for healthy volunteers.
- Investigators and IRBs should address risks beyond those that directly impact human subjects, since harms to family members, communities, or the public at large may erode trust.
- Institutions or sponsors should compensate human subjects for their injuries, since failing to provide subjects with medical treatment or some of other form of compensation when they are injured is unfair and may undermine trust in research.

12.4 Trust and Benefits

- Human subjects expect that investigators will share clinically useful individual research results with them. Failing to share these results in a timely fashion can undermine trust.
- Disclosing individual research results with uncertain clinical or practical values could positively or negatively impact trust. The decision to disclose individual research results should be made on a case-by-case basis, taking into consideration contextual factors, such as the study design, the benefits of disclosure, the population's ability to deal with uncertainty, and the costs of disclosure.
- It is appropriate to provide ancillary care to subjects in some situations to maintain and promote their trust. Decisions to provide ancillary care should be made on a case-by-case basis, taking into account various contextual factors, such as the population's health care needs, resources and expectations; the costs of ancillary care; and the depth of the relationship between investigators and subjects.

- Making provisions for post-trial access to anti-retroviral therapy (ART) in resource-poor settings is important for promoting trust in investigators, institutions, and sponsors, since HIV/AIDS patients who no longer have access to ART when a clinical trial ends may feel abandoned, exploited, or betrayed. Sponsors should offer to temporarily pay for post-trial ART until local governments and other parties can cover these costs. Priority should be given to providing ART to subjects who developed HIV as a result of their participation in the study. If sponsors do not have funds to pay for post-trial ART, or paying for treatment outside of a study is not part of their mandate, then investigators and institutions should work with other stakeholders to provide post-trial access to HIV care.
- Institutions and sponsors should provide communities, populations, or nations with a fair share of the benefits of research in order to promote their trust. Fair benefit-sharing is especially important when there is a historical record of exploitation of the community, population, or nation.

12.5 Trust and Vulnerable Subjects

- Since some of the worst abuses of human subjects have occurred to vulnerable subjects, to promote the public's trust in research, studies should include special protections for children, mentally disabled persons, prisoners, and other vulnerable groups. The default position should be that members of vulnerable groups should be excluded from research unless there is a legitimate scientific reason for including them.
- The public may lose confidence in research if research programs are not addressing the needs of members of vulnerable groups. For example, for many years women were routinely excluded from clinical trials to protect fetuses from harm. Trust can therefore be a double-edged sword, favoring both protection from harm/exploitation and inclusion in research (where appropriate).
- There are three types of vulnerability: (a) vulnerability related to impaired decision-making, (b) vulnerability related to risks; and (c) vulnerability related to the potential for exploitation. Some subjects, such as children, may meet all three conditions.
- To promote trust in non-beneficial pediatric research, investigators and IRBs should follow risk standards which are comparable to relevant community standards for children's risks. The risks of daily life is one such community standard for children's risk exposure in non-beneficial research. Another is a comparable age-appropriate community service activity, such as a working for Habitat for Humanity. Children can be exposed to risks in non-beneficial research not greater than the risks children typically are exposed to in comparable age-appropriate community service activities.
- Because the death or severe injury of a mentally disabled individual in a non-beneficial experiment could have a detrimental impact on the public's trust in research, the default position should be that adults with mental disabilities or

diseases that impair decision-making should not participate in more than minimal risk, non-beneficial research unless they have executed an advance directive expressing a desire to do so or there are compelling scientific reasons for including them in research.
- Because some women may need to take medications during pregnancy, it may be appropriate to included pregnant women in Phase II or III drug trials in some cases to promote women's health. Investigators should take appropriate measures to minimize risks to women and the fetuses when enrolling pregnant subjects in drug studies and to ensure that risks are reasonable in relation to benefits.

12.6 Trust and Research Integrity

- Investigator behavior is probably the single most important factor in protecting the rights and welfare of human subjects. Investigators (and research staff members) have direct contact with human subjects and therefore have the greatest opportunity to either help or harm them. IRBs, institutions, and sponsors must therefore trust that investigators will act responsibly and comply with regulations, guidelines, and policies.
- Investigator misbehavior can negatively impact the public's trust in research by (1) harming human subjects or violating their rights, (2) leading to fraudulent, erroneous, or biased results that cause harm to society or increase the risk of harm; or (3) wasting public resources.
- Investigator misbehavior may also erode researchers' trust in each other. Scientists must be able to trust, for example, that they can rely on published research results; collaborators will not steal their ideas, data, or methods; they will receive proper credit for their accomplishments; and that reviewers will evaluate their work fairly and respect the confidentiality of the peer review.
- Academic institutions, public and private research sponsors, and scientific journals should develop policies, procedures, administrative structures, and educational programs to prevent investigator misbehavior and deal with problems effectively and fairly when they occur. Leadership, mentoring, auditing, and accreditation can also play a key role in promoting research integrity.
- Policies, procedures, and administrative structures should address research misconduct, noncompliance, conflicts of interest, and publication or sharing of data.

12.7 Regulatory Reform

- Since the 1990s, national commissions, investigators, and bioethicists have made various proposals for reforming the U.S. research regulations. On January 19, 2017, federal agencies announced revisions to the Common Rule intended to: (1) reduce regulatory burden and (2) improve protections of human subjects. Some

of these changes (such as expending exemptions, limiting continuing review, and the single IRB mandate for cooperative research) reduce regulatory burden, while others (such as informed consent enhancements) improve protections for human subjects.

- While enhancements to the consent process could promote trust by providing human subjects with more information, the single IRB mandate has the potential to undermine subjects' and the local community's trust, because they may feel alienated from a remote IRB overseeing the research.

In closing, I will note that many of the findings and recommendations I have made in this book are based, in part, on empirical premises concerning the relationship between decisions, actions, policies and trust. Many of my arguments take the form of "We should do X because X promotes trust" or "We should not do X because X undermines trust." In some cases, I have cited data from published studies to support these conclusions. In other cases, my arguments are based on anecdotes, informed speculations, or unproven assumptions. I readily admit that this is a potential weakness of my view and acknowledge that more empirical inquiry is needed on the nature of trust in research with human subjects and how best to promote it. It would be useful, for example, to conduct more interviews with human subjects, members of specific groups, or the general public concerning the factors that impact their trust in investigators, institutions, and sponsors. As we gather more evidence concerning trust in research with human subjects, we should be able to develop a better understanding how best to protect the rights and welfare of human participants while advancing scientific knowledge.

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