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David B. Resnik

The Ethics of Research with Human Subjects

Protecting People, Advancing Science, Promoting Trust

Second Edition

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Contents

Abbreviations

AAMC	Association of American Medical Colleges
AAHRPP	Association for the Accreditation of Human Research Protection Programs
AI	Artificial intelligence
ARD	Advance research directive
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
COVID-19	Coronavirus of 2019
DHHS	Department of Health and Human Services
DMC	Decision-making capacity
DNA	Deoxyribonucleic acid
DOD	Department of Defense
DSMB	Data and Safety Monitoring Board
EU	European Union
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GFPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accessibility Act
HIV	Human immunodeficiency virus
HRPP	Human Research Protection Program
IRB	Institutional Review Board
LAR	Legally authorized representative
NASA	National Aeronautics and Space Administration
NBAC	National Bioethics Advisory Commission
NIH	National Institutes of Health
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
SACHRP	Secretary's Advisory Committee on Human Research Protections
SOPs	Standard operating procedures
SUPPORT	Surfactant, Positive Pressure, and Oxygenation Randomized Trial
UP	Unanticipated problem
WMA	World Medical Association

Chapter 1
Introduction

Abstract Research with human subjects 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. This chapter introduces the reader to a philosophical framework for thinking about these conflicts and issues. The framework, which will be described and defended in greater depth in subsequent chapters in the book, is grounded on widely accepted moral principles and the ethos of trust. The chapter also discusses seven controversial cases that serve to illustrate the importance of developing a philosophical framework for thinking about the ethics of research with human subjects. Cases discussed in the chapter include perinatal HIV prevention trials, the SUPPORT study, the Facebook deception study, xenotransplantation experiments, COVID-19 challenge studies, and the Henrietta Lacks case.

Keywords Ethics · Human subjects · Regulation · Trust · Oversight · Philosophy · Ethical dilemmas

Research with human subjects exemplifies the perennial conflict between the good of the individual and the good of society.[1] Policies and procedures that protect the rights and welfare of human subjects may hinder scientific research that benefits

[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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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. Every few months, a new issue, problem, or scandal enters the media spotlight and elicits predictable responses from concerned citizens, compliance officials, attorneys, and investigators. Concerned citizens, compliance officials, and lawyers often react by calling for additional regulation, oversight, or liability, while investigators usually respond to this familiar refrain 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 goal of this book it to shed some light on these recurring dilemmas and help society move toward practical solutions by developing a framework for thinking about research with human subjects grounded on widely-accepted moral principles and the ethos of trust. To better understand the value of such a framework, let's consider the following cases that illustrate some of the types of ethical problems and issues that arise in research involving human subjects.

1.1 Perinatal HIV Prevention Trials

In the 1990s, many developing[2] 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

[2] In this book I will use the term 'developing nation' to refer to nations classified as 'least developed' by the United Nations (2023). I realize that word-choice matters here and that there are different ways of referring to groups of nations, such as "low- and middle-income countries," "poor countries," or "global south countries" (Kahn et al. 2022). I find the idea of economic and industrial development to be more useful than these other terms for discussing research ethics issues, because degree of ethical/regulatory oversight tends to be positively associated with development status. By referring to a nation as 'developing' or 'developed' I do not mean to imply any moral judgement about that nation.

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).[3]

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[4] 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 three of the trials, including two 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 critique. Angell compared the trials to the infamous Tuskegee Syphilis study[5] 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 since it would involve detecting smaller differences between treatment groups.[6] 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).

[3] 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.

[4] Some philosophers hold that 'ethics' refers to the standards of conduct for a particular group or profession, e.g., 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. Using a philosophical distinction which does not reflect common practice may be confusing to readers not schooled in this particular way of speaking.

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

[6] The sample size needed 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 required sample size (Blair and Taylor 2007).

The controversial HIV prevention studies involved 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 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 (Dabs 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 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

Another example of the conflict between the rights and welfare of individuals and the common good occurred in 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 of 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).[7] The Common Rule,[8] which has been adopted by 19 federal agencies, requires that research subjects or their representatives be informed about reasonably foreseeable risks (Department of Health and Human Services 2017 at 45 CFR 46.116 b2). 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 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

[7] NIH is an agency within DHHS.

[8] Unless noted otherwise, references to the Common Rule used in this book will be to the 2017 revision. I will discuss the federal regulations in more depth in Chap. 2.

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 increased 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 considerable 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,[9] 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 2017 45 CFR 46.116f)." 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

[9] See Chap. 2 for discussion of exempt research.

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).

1.4 Henrietta Lacks

A widely used 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 since the mid-1950s. Journalist Rebecca Skloot (2010) became curious about this anonymous cell line and wanted to learn whom it came from. She discovered that Henrietta Lacks, an African American woman who underwent treatment for cervical cancer at Johns 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' left over tumor tissue without her consent, which was at that time 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 left over from medical procedures or tests.

Skloot also learned that Lacks' family received no financial compensation for the tissues, which was also not unusual. Skloot's book became a popular best-seller, *The Immortal Life of Henrietta Lacks*, which was later made into a film. Skloot decided to donate some of the profits from the book and film to a non-profit foundation she established, the Henrietta Lacks Foundation (2017), which provides support to individuals and families adversely impacted by research without consent. 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). In 2023, the Lacks family reached a legal settlement with Thermo Fisher, a company that profited from selling Hela Cells to researchers and research institutions (Wadman 2023). Another lawsuit against Ultragenyx Pharmaceuticals is still being litigated (Dye and Menikoff 2024).

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

The Lacks case focused national attention using biological specimens in research, which also can involve a conflict between the rights of individuals and the good of society. Proposed revisions to the Common Rule published in 2015 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]

It almost impossible to think about the Lacks case without considering its racial implications (Merelli 2023). As will be discussed at greater length in Chap. 2, African Americans have often been the victims of unethical and exploitative experiments, such as the Tuskegee Syphilis Study, and the Lacks case belongs to this historical pattern. However, while although Lacks was exploited by researchers and private companies, it is not clear that she was exploited because of her race, since it was common practice at that time to use left over tissue for research without obtaining consent. Indeed, in Chap. 2, we will a very similar case involving a white man, John Moore.

1.5 The Facebook Behavioral Manipulation Experiment

Informed consent was also a major concern in a social psychology experiment conducted using the social network Facebook in 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 *Proceedings of the National Academy of Sciences* 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 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

[11] We will discuss consent for the use of biological specimens in more depth in Chap. 5.

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 2022). Some have argued that the U.S. should close this gap in the federal regulations to ensure uniform protections for all human subjects (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 2008).

1.6 COVID-19 Challenge Studies

In the fall of 2019, a virus named SARS-CoV-2 (sever acquired acute respiratory infection, coronavirus 2) spread quickly from Wuhan, China to the rest of the world and caused a global pandemic. Over seven million people died from COVID-19 (coronavirus disease of 2019) and hundreds of millions of people became seriously ill or were hospitalized. COVID-19 caused a public health crisis on a scale not seen since the 1918 Spanish flu pandemic. (World Health Organization 2024).

When the pandemic began, there were no effective treatments or vaccines for COVID-19, so most countries implemented draconian public health policies, such as closures of schools and businesses, curfews, and travel restrictions, to try to stop the spread of the disease and save lives (Resnik 2021). It soon became clear that COVID-19 posed a far greater threat to people who were elderly or infirm than to those who were young and healthy. While the case fatality rate for people 80 years old or older was nearly 15%, the case fatality rate for children was less than 0.5%, and most of the children who died from the disease were already seriously ill (Wu and McGoogan 2020). Most children and young adults who contracted COVID-19 experienced mild symptoms or none at all (Resnik 2021).

Although vaccine clinical trials began in the spring of 2020, they were not expected to be completed until later in the year, and vaccines were not likely to be widely available until early 2021. Vaccine trials normally take from 12 to 18 months

to complete because investigators must wait until enough people have been exposed to the pathogen as a result of normal life activities so that statistically valid comparisons can be made between experimental and control groups (Resnik 2021).

In light of these circumstances, some scientists and ethicists argued that researchers should accelerate the vaccine development process by conducting studies that intentionally expose healthy, young volunteers to COVID-19. The volunteers, who would not have previously had COVID-19, would receive a vaccine or placebo before being inoculated with the virus. The purpose of these studies would be to identify promising vaccine candidates and cut months off the time needed to develop an effective vaccine (Eyal et al. 2020). Proponents of these studies argued that the risks imposed on volunteers would be justified in terms of the potential benefits. The risks of death or serious hospitalization for the study population, though not trivial, would still be orders of magnitude lower than the risks for general population or vulnerable groups. Proponents argued that the trials could potentially save thousands of lives, even if they shortened the length of vaccine development by only a few weeks (Eyal et al. 2020). When this proposal became widely known, thousands of people said they would volunteer for these studies to help in the fight against COVID-19. A non-profit organization, 1Day Sooner (2024), was formed to promote participation in vaccine challenge trials to accelerate the development of vaccines and treatments for infectious diseases. The World Health Organization (2020) developed criteria for ethical acceptability of COVID-19 challenge studies.

However, there was—and still is—significant opposition to these studies.[12] Critics argued that these challenge studies were too risky, especially since there were no effective treatments for COVID-19 at the time; that the benefits of the studies were speculative; and that exposing healthy volunteers to a dangerous virus as part of a medical experiment could undermine public trust in research if people died in the study (Kahn et al. 2020).

Although vaccine developers, such as Pfizer, Moderna, Johnson and Johnson, shied away from sponsoring COVID-19 challenge studies, the UK government did not. In the fall of 2020, the UK Vaccine Taskforce approved the funding of COVID-19 challenge studies. When the first COVID-19 vaccines were approved in early 2021, many argued that the COVID-19 challenges studies were no longer needed. Others argued, however, that there were still compelling reasons to do challenge studies, since these experiments could provide useful information about the pathophysiology of the disease and its clinical manifestations under controlled conditions (Eyal 2024).

In May of 2022, researchers from the Imperial College of London published the results of the first COVID-19 challenge study (Killingsley et al. 2022). In the study, 34 volunteers (age 18–30) were inoculated with COVID-19. 53% of the participants became infected, with a peak viral load occurring within five days of exposure. Of these, 89% experienced mild to moderate symptoms and 11% had no symptoms. There were no serious adverse events (Killingsley et al. 2022). According to the

[12] In Chap. 7, I will examine the ethics of these and other challenge studies in greater depth.

investigators, the study helped to better establish "viral kinetics over the course of primary infection with SARS-CoV-2" which has "implications for public health recommendations and strategies to affect SARS-CoV-2 transmission (Killingsley et al. 2022: 1031)." In September 2024, the investigators published the results of cognition and memory tests performed on the volunteers at 30, 90, 180, 270, and 360 days. The investigators found that infection with SARS-CoV-2 was associated with small deficits in memory and cognition that persisted for at least a year. The participants earned up to $6100 for completing the study (Trender et al. 2024). Investigators at the Imperial College of London (2024) are currently recruiting healthy volunteers for COVID-19 challenge studies. Some have argued that the debate about the COVID-19 challenge studies represents an important turning point in vaccine development policy and that, in the future, challenge trials may become an accepted method part of the vaccine development process (Eyal 2024).

1.7 Xenotransplantation Experiments

On January 7, 2022, surgeons at the University of Maryland School of Medicine performed the world's first pig-to-human heart transplant on David Bennett, a 57-year-old male with heart disease. Although the operation was initially deemed a success, Bennett's condition deteriorated, and he died on March 9, 2022 (Wang et al. 2022; Associated Press 2022). The heart Bennett received came from a genetically modified, "humanized" pig. The pig's genome had been modified to code for human cell-surface proteins, which would make its organs less likely to be attacked by the human immune system (Wang et al. 2022). The FDA authorized the procedure under its expanded access, compassionate use provisions, which allow the agency to approve an experimental device that has not undergone clinical trials for a patient with a life-threatening medical condition for which there are no available alternative treatments (Singh et al. 2022; Food and Drug Administration 2024). This was not the first time that doctors had performed cardiac xenotransplantation on a human being. In 1984, an infant in California known as Baby Fae lived for 21 days after receiving a baboon heart (Associated Press 2022).

Since about 5600 people in the US die each year while waiting for a new organ (Donate Life America 2024), research on the use of humanized pig organs for transplantation offers substantial benefits for society. However, the research raises several ethical concerns (Johnson 2022). First, pigs carry endogenous viruses that could infect organ recipients and enter the larger human population. Although these viruses might not cause the pigs any health problems, because the pigs have developed immunity to them and/or have evolved to live with them, the viruses could be very dangerous to human beings, who probably lack immunity (Rollin 2020). As the world learned during the COVID-19 pandemic, zoonoses (i.e., animal diseases that can infect humans) pose a major threat to humanity. Although researchers are taking various measures to minimize the risk of zoonoses, such as testing pigs for viruses and rearing them in sterile environments, these risks cannot be eliminated

entirely. The U.S. research regulations (discussed in Chap. 2) focus on risks to subjects and do not provide the IRB with guidance on how to address societal risks related to research. In Chap. 7, we will consider the issue of whether (and how) IRBs should address these risks.

Second, to protect the human population from risks of zoonoses, organ recipients must agree to lifelong monitoring, which raises issues concerning the validity of consent, since recipients may not fully understand the implications of this monitoring, and the enforceability of the consent agreement, since it may be difficult to locate or control recipients who decide to shirk their responsibilities (Johnson 2022).

Third, the research raises animal welfare concerns because the pigs will be killed to harvest their organs. People who oppose killing pigs for food may also oppose killing pigs for medical purposes (Rollin 2020). Animal welfare concerns are not addressed by the US human research regulations and there are not unique to xenotransplantation. Most new drugs and medical devices are tested in animals before they are tested on people (Shamoo and Resnik 2022).

Fourth—and this issue is also not unique to xenotransplantation—the research raised issues about experimenting on brain-dead people, since pig organs were tested on brain-dead patients first (Associated Press 2023).[13] Research on brain dead people raises challenging ethical and regulatory questions because U.S. research regulations (discussed in Chap. 2) apply only to living individuals. Since research on brain-dead people falls outside the jurisdiction of the IRB, there are questions about how it should be overseen. In the absence of a clear legal framework for research on brain dead people, some institutions have formed special committees to review this research or asked IRBs to review it (Madhusoodanan 2024).

1.8 Overview of This Book

As one can see from the cases discussed above, research with human subjects raises complex and controversial ethical, social, and legal issues. In most of these cases, conscientious and well-informed scientists and bioethicists reached different conclusions concerning ethical and regulatory questions being raised. 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.

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

[13] A brain-dead person is an individual whose brain that no longer functions. In the U.S. and many other countries, brain-dead people are legally dead. However, their bodies can be kept alive by means of medical technology.

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 disagreements were also about the kinds of policies and oversight systems that should be in place to protect human research subjects. The overarching issue—the good of individual versus the common good—impacted these disputes explicitly or implicitly. Scientists and bioethicists came down on different sides of the issue, with some emphasizing the importance of protecting research subjects and others the importance of advancing scientific knowledge and benefitting society. 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 the resolution of 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 and wellbeing 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. 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.

Some argue 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.

Some philosophers are skeptical of the entire project of developing a philosophical framework for thinking about the ethics of research with human subjects. According to Alan 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).

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" in any deep sense, it should provide us with some guidance concerning ethical and policy dilemmas.

When I wrote the first edition of this book in 2017, there were very books on the ethics of research with human subjects that developed a comprehensive, philosophical framework for thinking about the issues and dilemmas.[14] There were articles, anthologies, and guidance documents that discussed the foundations of research ethics, but there were no books on the subject.[15]

Four years after my book first appeared in print, Alex London (2022) published a well-received book on the philosophical foundations of ethical research with human subjects.[16] In this book, London argues that (1) scientific research is a cooperative enterprise that should promote common societal goals and (2) the current system of regulatory oversight should be reformed to better reflect a commitment to the common good. According to London:

> Research is a scheme of social cooperation that serves a public purpose grounded in considerations of justice. One such consideration of justice concerns the claims that community members have on the goals and ends that are advanced by the research enterprise. Following the egalitarian research imperative, the public purpose of research is to generate the knowledge necessary to bridge gaps in the capacity of the basic social institutions of a community—such as its system of public health and clinical medicine—to safeguard and advance the basic interests of that community's members (London 2022: 251–252).

While I think London's book provides readers with some valuable insights, I believe my book still has considerable value as an alternative to London's for two reasons. First, London's book is highly idealistic and abstract and does not adequately deal with the historical, economic, political, and social aspects of modern science, or practical matters related to IRB review, research oversight, informed consent, study design, methodology, and research integrity. My book is more pragmatic than London's and encompasses both theory and applications. Second, the theory London defends in his book is based on an egalitarian approach to questions of morality and political philosophy. While egalitarianism is a highly respectable and influential philosophical theory (see discussion in Chap. 3), it is also controversial, because it entails restrictions on individual rights and redistribution of wealth to achieve egalitarian social goals, such as equality of opportunity and social justice (Arneson 2013). As a result of his strong commitment to egalitarianism, London does not

[14] Some books worth mentioning include books by Veatch (1987), Levine (1988), Brody (1998), and Wendler (2010). Each of these books has strengths and limitations. Veatch's depicts research as a partnership between the subject and investigator but does not say much about what that partnership involves. Levine provides useful guidance related to interpreting and applying ethical rules and the U.S. federal regulations but does not provide a philosophical foundation for these rules and regulations. Wendler describes and defends a philosophical framework for thinking about the ethics research on children, but it is not clear how the framework does not extend far beyond pediatric research.

[15] Three excellent collections of articles include Emanuel et al. (2008), Coleman et al. (2015), and Iltis and Mackay (2024).

[16] Elsewhere (Resnik 2022), I have published a review and critique of London's book.

adequately consider opposing views of the common good, which weakens his analysis of contested topics in research ethics, such as the commercialization of research, using placebos in research, and ancillary care obligations. The approach I defend in this book is likely to have greater appeal than London's because it is grounded on widely-accepted ethical notions, such as the *Belmont* principles (discussed in Chap. 2), and the idea of trust (discussed on Chap. 4).

My plan for the books is as follows. In Chap. 2, I will describe the historical events that have shaped ethical rules and policies concerning research with human subjects. I will 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 that can help us deal with ethical and regulatory 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' (2019) 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, we require some additional guidance for dealing with ethical and policy dilemmas.[17]

In Chap. 4, I will describe and defend my trust-based approach. 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. Although promoting trust does not solve all ethical dilemmas in research, it can be an essential tool in helping us to develop workable solutions.

In Chaps. 5, 6, 7, 8, and 9, I will apply the trust framework to ethical issues in research with human subjects, including:

- Obtaining and documenting informed consent
- Determining whether a person has the capacity to consent
- Conducting research without consent

[17] 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).

- Using general (or blanket) consent forms
- Using opt-out consent procedures
- Deceiving research subjects
- Paying people for research participation
- Safeguarding privacy and confidentiality
- Sharing data and biospecimens
- Assessing and balancing risks and benefits
- Minimizing risks
- Defining minimal risk
- Choosing the appropriate clinical trial design (e.g., whether to use a placebo control group)
- Conducting challenge studies on healthy volunteers
- Upper limits for risks to healthy volunteers
- Dealing with risks to third parties, communities, and society
- Sharing individualized results with research participants
- Sharing research benefits with subjects, communities, and populations
- Providing ancillary care to subjects and post-trial access to medications
- Enrolling and protecting vulnerable subjects in research
- Issues with special populations, such children, pregnant people, and adults with impaired decision-making capacity
- Promoting research integrity
- Investigating and reporting misconduct and non-compliance
- Disclosing and managing conflicts of interest in research

In Chap. 10, I will summarize the book's main arguments and conclusions and discuss some proposals for reforming the current oversight system and areas of further study.

Before proceeding further, two caveats are in order. First, policy discussions in the book will focus, for the most part, on U.S. regulations, and, to a lesser extent, on regulations in other countries and 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 2024). Moreover, the U.S. and other countries are dealing with similar issues, and the standards adopted in the U.S. have considerable international influence (Brody 1998). 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. Third, the opinions expressed in this book are my own and do not represent the views of the NIEHS, NIH, DHHS, or U.S. government.

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