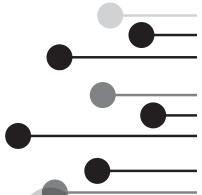


CHAPTER
1

Understanding Why You Submit an IRB Protocol for Review of Your Research Plans



Chapter Purpose

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A central question about your research forms the focus of this chapter: Why do you need to request IRB approval for your project? This initial chapter contextualizes the work of the book by situating historical abuses and current policies related to protections for human research participants. The chapter unfolds by descriptively detailing and linking ideals from the *Nuremberg Code* and *Declaration of Helsinki* to IRB protocol review today. Later in the chapter, I tie abuses with human research participants in medical experimentation by US officials and/or in US institutions of higher education or government agencies to what grew out of them: an early US regulatory framework in the *Belmont Report* that governs human subjects research today. The chapter focuses on provisions in the Common Rule and what 45 Code of Federal Regulations Part 46 means for readers in terms of federal policy and general IRB principles that govern campus protocol review. The chapter ends by considering the role of state- and institution-level policies of human research participant protections and research governance.

A Brief History of Abuses of Human Research Participants in Biomedical Research in the 1920s–1950s

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Why IRB? When you work with humans in your research work, why do you undergo review of your research plans? Why do your proposed recruitment procedures, data collection instruments and procedures, data storage and management protocols, details of possible risks and benefits

Learning Objectives

- Contextualize current Institutional Review Board (IRB) practice in historical events and link what you do today in research governance and review of research protocols to human research participant abuses
- Describe specific IRB concepts, with a focus on voluntary participation and consent, that emerged from the *Nuremberg Code* and *Declaration of Helsinki*
- Link principles of human research protections in the *Belmont Report* and the Common Rule or 45 Code of Federal Regulations Part 46—respect for persons, beneficence, and justice—to IRB protocol requirements

to participants, and potential outcomes of the study need to be approved by a panel of peers, experts, and community members? Let's face it, you tend to share a lot of detailed information about your study in the IRB review process—and doing all of this work early in a study may be intimidating or challenging. In some cases, your ideas about a study may still be evolving and not all of the potential issues with your recruitment or data collection procedures may be set yet. Submitting a study still in the proposal phase may subject your work to scrutiny for which you are not ready and that may result in changes to what you do in your project—ready for changes or not.

As you start a research project where people will be a part of what you do in the study—from whom and with whom you will gather and make sense of information—these are common questions and concerns. Especially at the start of a research career—as an undergraduate student, graduate student, or early career faculty or university researcher—questioning why you have to undergo IRB review is not unusual. As you explore historical and current disciplinary conventions related to research, changing epistemological and methodological approaches in the field, and standard and emerging approaches that guide data collection and analysis, you may wonder why you are subject to research governance on your campus.

The process that you follow and the requirements to which you conform for approval of your research plans with human participants are neither arbitrary nor unnecessary. Indeed, they form part of a research governance system that emerged as a response to abuses with human biomedical experimentation and experimental conditions in social and behavioral science studies. While researchers may argue that they are an inconvenient step in the research process, an overreach of government or campus authority, and/or misguided efforts to shield groups from undue influence, regulatory structures that inform research review and approval generally do what they are meant to do: protect people who participate in research studies (and protect institutions from liability associated with research studies conducted on campus/under the auspices of the institution). While current regulations and systems of research governance need revision, they are still generally necessary to implement policies to protect individuals from abuse and mistreatment—even if unintentional—in the research process. In fact, recent updates and revisions to the Common Rule point to a general need to reshape regulations to address problems in research review and balance the need to efficiently approve research projects while protecting research participant rights, which have been developed as a response to worldwide abuse.

Systematic Abuses in Human Experimentation in Germany and Japan

As a general pattern, documented cases of human experimentation in biomedical studies tend to parallel military conflict, the rise of autocratic regimes, and/or the colonizing campaigns of Western powers over the course of the 20th century. Indeed, leading up to, during, and following World War II, military rule in countries

around the world perpetrated abhorrent abuses of human research participants in experimental studies in medicine. These states sanctioned the misuse and maltreatment of people as experimental subjects under the guise of biomedical research—and the aftermath of their atrocious, horrid mistreatment of humans in experiments generally led to the documentation, codification, and eventual use of ethical principles and research governance rules to protect individuals in research work.

In the context of World War II, the charging documents and opening statement of the prosecution at the Nazi doctors' trial in 1946–1947—where German biomedical researchers were tried for conspiracy, war crimes and crimes against humanity, and membership in a criminal organization—you can see experiments that resulted in extreme pain, suffering, and frequently death of hundreds of thousands of individuals. Often conducted on small groups—and at times on larger scales—these experiments ranged from investigations of the effects of vaccinations on disease and wound care from battlefield injuries to poisoning of Russians and racial cleansing and extermination through sterilization of “Russians, Poles, Jews, and other people” (Taylor, 1992, p. 79) and Jewish skeletal examinations. As you can see in the callout box, the volume and scope of these experiments underscore their atrociousness, viciousness, and destructiveness on entire groups of people and, more broadly, humanity. With clear, compelling and convincing evidence and heartbreaking accounts of abuse and horror in human experimentation, Fins (2014) shares a poignant observation that Nazi doctors lacked a total “respect for the individual, so cruelly distorted by an errant ideology and an evil perversion of science” (p. 280).

While widespread, systematic abuse of humans in several hundred experiments marked Nazi Germany during World War II, these programs could be seen in Japan, too. As part of prewar and wartime programs of human experimentation, units of the Imperial Japanese Army set up sites where prisoners of war (POWs) were subjected to involuntary injections of infectious diseases in vaccination trials, effects of chemical/biological weapons, and surgical experiments.

Experiments Sponsored, Designed, and Conducted on Human Participants in Nazi Germany (Taylor, 1992)

- Effects of exposure to high-altitude and low-pressure, where people were forced into chambers and intentionally exposed to varying conditions of air pressure
- Treatment effects of malaria with intentional injections on individuals
- Effects of mustard gas exposure on intentionally inflicted/simulated burn wounds

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- Experiments with intentional infliction of battlefield wounds and injuries to test the effects of sulfanilamide, an antibiotic
- Experiments in nerve regeneration, blood coagulation, bone transplantation with intentional removal and placement of bones from one person to another
- Experiments with drinkable seawater where individuals were not allowed to drink any water, forced to drink treated and untreated seawater (with salination), and desalinated seawater; epidemic
- Experiments to develop a vaccine for epidemic jaundice with intentional infectious injection of individuals
- Drug and surgical sterilization experiments, as part of a genocidal program to exterminate “Russians, Poles, Jews, and other people” (Taylor, 1992, p. 79)
- Vaccination experiments for typhus, smallpox, cholera, etc., involving intentional injection of the disease on individuals
- Poison experiments, where Russian prisoners of war were given poisoned food and/or shot with poisoned bullets
- Incendiary bomb experiments, which included direct and intentional infliction of burns on individuals
- Research carried out under the guise of anthropology where Jewish skeletons, particularly skulls with brains intact, were examined as part of a program to promote Nazi racial theories of German racial superiority

Whatever the focus of the experiment across national contexts during the war, all of these activities shared several common features, including:

- Statutory and/or policy authorization of—or absence of specific statutes or policies prohibiting—experimental activities;
- Official and/or implicit government/military/public program of racism, racial superiority, racial cleansing, genocide, sexism, and/or ableism;
- General support and coordination of experiments from high-ranking government and/or military officials;
- Funding and staff support for experiments to be conducted;
- Specific roles for research and medical staff, including physicians, in experiments;
- Absence of voluntary consent from and/or forced or coerced participation of humans;
- Lack of assessments of risk-benefits to participants and patent disregard for the human dignity of participants;

- Brutal, violent, painful physical acts against individuals, including injection of infectious disease, dismemberment, disfigurement, and death; and
- Absence of remorse or culpability from immoral, unethical and criminal actions committed under the guise of rigorous, systematic, scientific investigations.

As detailed here and below, in accounts of abusive, atrocious experiments with human research participants associated with Germany and Japan, many—if not all—of these features appeared in one form or another in the United States, and elsewhere, too.

Early World Response: The *Nuremberg Code* and *Declaration of Helsinki*

As military conflict ended in Europe and Asia and attention in the aftermath of World War II turned to prosecution of war crimes, one of the areas of focus for American military operations was the military personnel and doctors who perpetrated experiments on humans, as part of official racial cleansing and genocide in Germany. Established under the US Military Government for Germany and convened from October 1946 until August 1947—with sentences carried out by June 1948—the trial known as “The Case Against Nazi Physicians” (Annas & Grodin, 1992) or simply the Nazi doctors’ trial, detailed the horrific experiments that physicians and medical researchers designed and conducted.

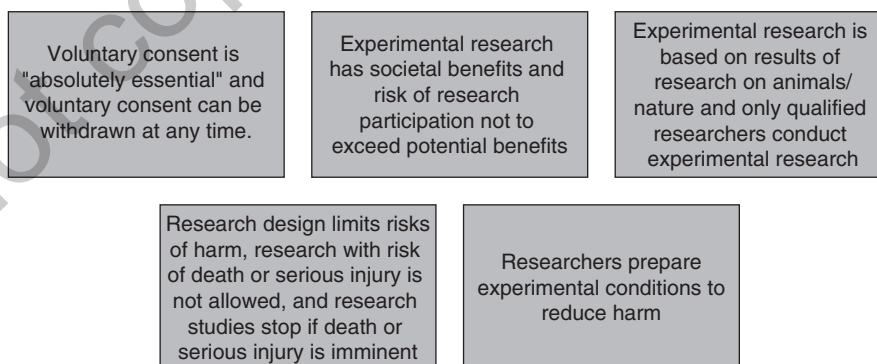
What the doctors’ trial at Nuremberg accomplished extended beyond principles for the ethical treatment of people in experimental trials; the trial restored a sense of humanity in humans who participate in research—especially experimental research in the biomedical sciences. And while principles that emerged from trial may not have been widely adopted in research communities at the time, they have had a lasting and profound effect on what we do now in research. As the judicial proceedings ended, a set of principles emerged from expert testimony at trial and included a final record at trial for the Nazi doctors. Where did principles in the code originate? Grodin (1992) explains that the Hippocratic Oath, with a focus on patient benefits, served as a founding framework for the principles in the *Nuremberg Code*. In addition, both Thomas Percival, English physician, and William Beaumont, American surgeon with the US Army, developed codes of ethics that appeared to inform principles in the *Nuremberg Code* (NIH, n.d.; Grodin, 1992). While the American Medical Association’s Code of Medical Ethics generally informed expert testimony at trial, the initial set of ethical principles did not include medical experimentation (Grodin, 1992). Beyond historical origins and then-contemporary ideas about human experimentation in medical research,

Brody (2014) reports that a 1898 human experiment with injections of gonorrhea bacteria into sex workers without their consent led to an investigation, finding, and later codification in German law that human research participants must consent to procedures—and this German law remained on the books during World War II.

Eventually numbering 10 total, the principles that formed the *Nuremberg Code* (NIH, n.d.; Annas & Grodin, 1992) can be summarized as follows (and in Figure 1.1):

1. Voluntary consent—with legal capacity to consent—of human subjects is “absolutely essential.”
2. Experimental research should have societal benefits.
3. Experimental research should be based on results of research on animals and the natural world.
4. Experimental research design should limit risks of harm to human subjects.
5. No experimental research should be conducted if researcher anticipates death or serious injury to human subjects.
6. Risk of research participation should not exceed potential benefits.
7. Researchers should prepare experimental conditions and facilities to reduce harm to human subjects.
8. Only qualified, trained researchers should conduct experimental research.

Figure 1.1 Thematic Grouping of Principles of the *Nuremberg Code*



9. Voluntary consent of human subjects can be withdrawn at any time during an experimental research study.
10. Researchers must halt an experimental research study if they believe death or serious injury to human subjects is imminent.

As you can see, the principles address ethical concerns and criminal behavior of the heinous, murderous experiments that involved humans as research participants sponsored and conducted by Nazi doctors. They would later guide the development of professional ethical standards by the World Medical Association (WMA) and the Common Rule regulatory framework by the US Congress as a response to abuses funded, coordinated, and executed by the federal government.

As an initial effort to self-regulate clinical trials in the biomedical research community, the *Declaration of Helsinki* modernized the 10 points of the *Nuremberg Code* and addressed them in the context of clinical trials in biomedical research. Initially written as a foundational set of guiding principles for researchers, the WMA adopted them at the 18th WMA General Assembly in Helsinki, Finland, in June 1964. Amended multiple times since adoption—1975, 1983, 1989, 1996, 2000, 2002, 2004, 2008, and 2013—the seminal work generally guides what we do today in research governance and review of research protocols in IRBs. Specifically, the 1975 revision focused on research governance by a committee—with subsequent revisions in 1983 and 1989 further clarifying committees. Looking back, you can see how the idea of committee review of research informed the work of the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the United States that resulted in issuing the *Belmont Report* that undergirds the Common Rule, or 45 CFR 46—the regulatory framework for human participant research in the United States.

The *Declaration of Helsinki* tends to focus on individual responsibilities of physicians and biomedical researchers in clinical trials that involve human participants, elevating the health, safety, and “right to self-determination, privacy, and confidentiality” of participants as the highest priorities in an investigation. Beyond guidelines that relate to participant safety, risk-benefits of participation, informed consent of participants, and requirements that studies meet research standards in the field, the *Declaration of Helsinki* presents a general process for research review and approval as follows:

The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified.

(WMA, 2013)

In the same article, 23, the *Declaration of Helsinki* offers general guidelines to institutions in their monitoring and final disposition of approved research protocols as follows:

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

(WMA, 2013)

Clearly, you can see here the foundation for current approaches to research governance and review under a system of IRBs. Both the *Nuremberg Code* and *Declaration of Helsinki* were conceptualized, and remain, as basic protections that apply to all human research participants in any study—and they encapsulate universal principles that researchers not just should but must follow if they work with humans as participants in their research. In fact, if you take a quick look at what we generally include in an informed consent form or bill of rights to experimental research participants, you can see many of these principles at work—from voluntary consent and withdrawal of consent to risk-benefits and minimizing risks to participants.

From Absolutely Essential in the Nuremberg Code to If at All Possible in the Declaration of Helsinki: The Idea and Practice of Voluntary Consent

One of the leading principles to emerge from the *Nuremberg Code* is voluntary consent—the notion that individuals must affirmatively agree to engage in a research activity or set of activities and cannot be coerced or forced to participate in a research study against their free will. What does voluntary consent mean? Emerging from the *Nuremberg Code*, the idea that voluntary consent, or freely and affirmatively agreeing, is an absolute that unequivocally means that researchers consent individuals prior to the start of participation in a research study. Later, in the *Declaration of Helsinki*, voluntary consent remained central to individual participation, but proxy consent could be considered if individuals could not consent on their own. From the most recent, 2013, revisions to the document, voluntary consent means “[p]articipation by individuals capable of giving informed consent as subjects in medical research” (WMA, 2013). Yes, consulting family members, elders, and/or community members may be appropriate—but consent can only be given freely by an individual who will participate in research activities. In cases where an individual cannot consent to participate—children, individuals

who are criminal justice-system impacted, individuals with impaired decision-making capacity—the *Declaration of Helsinki* guides researchers to “seek informed consent from the legally authorised representative” (WMA, 2013). In certain cases, especially with children, who may not be able to consent on their own, “the physician must seek that assent in addition to the consent of the legally authorised representative” (WMA, 2013).

In practical terms, IRBs require evidence that researchers consent participants in some way—to demonstrate that individuals understand that participation is voluntary—even if an IRB approves the use of a waiver of documented consent. Typically, documenting consent happens through the use of a written informed consent form, which includes provisions that affirm research participants’ rights and researchers’ obligations. [Table 1.1](#) lists general elements of a written informed consent form.

Table 1.1 Elements of Written Informed Consent

Element	Meaning in Context
Purpose of the study	What the study hopes to do and is about
Researcher(s) name and contact information	Name, mailing address, email address, and telephone number of researcher(s)
Participants—inclusions requirements	Eligibility criteria that researchers use to select participants
Time commitment	Time to complete each procedure and total time to complete all procedures in the study
Procedures	Specific data collection procedures (e.g., interviews, focus groups, critical incident reports, etc.) in which participants will engage
Benefits—participants	Individual benefits that participants can expect if they complete each/all procedures in the study
Benefits—society	Broader benefits to society associated with the study
Alternatives to participation	Additional options to participation, if any, for individuals if they elect not to participate in the study
Participant compensation	Remuneration offered to individuals who participate in the study
Costs (and reimbursement of costs) to participate	If costs are associated with participation, details about costs and if reimbursement for costs will be available

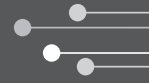
(Continued)

Table 1.1 Elements of Written Informed Consent (Continued)

Element	Meaning in Context
Withdrawal or terminations of participation and consequences	Notice that participants may end involvement in the study at any time and consequences, if any, for ending involvement in the study
Confidentiality—identifiable data	Specific provisions for managing identifiable, coded, and deidentified data
Confidentiality—data storage	Detailed safeguards of storing research data
Confidentiality—data access	Detailed information on who, including researchers, has access to research data
Confidentiality—data retention	Statement on how long research data will be retained
IRB contact information	For questions, comments, and concerns of research participants, IRB contact information, including physical location, mailing address, and telephone number
Voluntary participation statement	Statement of voluntary participation in all research activities and involvement in the study
Agreement to participate	Check box or acknowledgement of agreement to participate in the study
Agreement to be audio recorded (if applicable)	Check box or acknowledgement of agreement to be audio recorded
Agreement to be video recorded (if applicable)	Check box or acknowledgement of agreement to be video recorded
Signature—research participant	Signature line for research participants
Signature—researcher	Signature line for researchers

You can see that consenting research participants in written form is both intuitive—with a move from researcher information and study background to study procedures—and technical, with coverage of details of what participants will do in a study to specific risks and benefits of participation. Clearly, you must address core elements of informed consent, working to detail the parameters of research participation for your study in written form so that individuals whom you recruit have enough information to make an informed decision. What is sufficient information here? Well, the short answer is that all of the elements that you see in [Table 1.1](#) are essential to understand what it means to participate in a

Key Questions to Ask Yourself



How do consent form templates, if available, from your campus, compare to the elements of informed consent in [Table 1.1](#)? Jot down a few

notes from a quick comparison and share your observations with a colleague and/or an IRB compliance officer in your campus.

study. But if you relate principles from the *Nuremberg Code* and *Declaration of Helsinki* to written informed consent, you can focus on a statement of voluntary participation, a list of eligibility criteria to participate, a description of study procedures, a description of risks/benefits from participation, and the affirmation of participants. As a researcher, these are the elements that you need to clearly articulate and present to individuals whom you recruit and who are considering participation in the study. But consult your local IRB for exact requirements, templates or examples, and guidance on what needs to be included in consent forms.

As part of procedures to consent participants, you may need to use separate consent to use and/or release/publish video or photographic images. When you ask research participants to be the subjects of still or motion images, they agree to be recorded—their person, their likeness, their physical features. These images extend beyond personal and group interviews and/or ethnographic-type interviews in fieldwork settings, which tend to be limited to voice recording only. Here, agreeing to be audio recorded may be included or integrated into a written informed consent form with a simple checkmark or statement where participants affirm their agreement to participate in the study. Video or photographic consent may also be included in a general consent form—also with a checkmark or statement—but the nature of capturing individual or group images requires additional safeguards. These added measures protect participants from risks associated with the use and distribution of their images. In fact, a separate image consent form may include specific permissions to distribute or display images at scholarly or research publications, scholarly or research conferences, academic setting (e.g., classrooms), public presentations, television or film, and over the Internet—in websites. These specific permissions may include copyright permission to use the images. You can see that the unique nature of recording an image or images of someone or a group of people who participate in research requires an extraordinary approach to ensuring that folks understand to what they agree. [Table 1.2](#) presents specific information to consider including in a photographic/video image consent.

In some cases, researchers may not be able to document consent or may need to limit or alter written or recorded documentation of consent. Where consenting may put research participants at undue risk or harm or where risk is minimal and written consent may not be warranted, researchers may request a

Table 1.2 Elements of Photographic/Video Image Consent

Element	Meaning in Context
Title of project	Research study title
Researcher contact information	Researcher name, campus mailing address, campus email address and phone number
Collection of image/video research data	General statement about the nature of research data as video (motion) and/or photographic (still) images
Specific permission to use images	Participant permission for researcher(s) to publish, distribute, display and/or copyright images in potentially multiple formats, including but not limited to scholarly or research publications, scholarly or research conferences, academic setting (e.g., classrooms), public presentations, television or film, and Internet
Withdrawal of permission	Statement that participants may withdraw consent for release of images at any time
Acknowledgement	Statement that participant acknowledges reading and understanding specific permissions granted in the form, changing permissions need to be made in writing, and receiving a copy of the consent form
Statement of affirmation	Statement that participants agree to the conditions of consent in the form
Signature-research participant	Signature and date line for research participants

waiver or alteration of written informed consent or documentation of consent. Here, researchers may need to avoid obtaining consent, avoid documenting consent of participants, or alter consenting participants in some way. What study conditions may lead to altering or not documenting consent? In some cases, a data collection instrument or procedure makes written consent unnecessary or impractical—for example, a survey instrument generally justifies the use of a participant information form, a type of written consent that does not require participant signature or affirmation with a signature or in the presence of a researcher or researchers. In other cases, using deception in a study may

require changing the study background information in the consent process. Still in other cases, working with sensitive topics, like drug use or sexual activity, may pose immediate or extended economic, legal, social, and/or emotional risks to participants. In these instances, researchers can work to limit or avoid any documented link between personally identifying information like names when consenting participants.

Even in cases where documentation of consent does not occur, researchers still have obligations or requirements to consent participants. Indeed, researchers may request waiving the requirement to obtain informed consent or altering some or all of the elements of informed consent—where a researcher effectively does not obtain a signature to document consent. When researchers meet one or more of the conditions below, they may request—and be approved for—a waiver of documented or written informed consent:

- The US Food and Drug Administration (FDA) does not have regulatory oversight under 21 CFR 50 with the research study. That is, the study is not a clinical investigation regulated “under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products” (U.S. Department of Health and Human Services, 2017).
- The research study does not involve identifiable biospecimens or personally identifiable information.
- The research study presents no more than minimal risk—i.e., no more than what you encounter in everyday life—to participants.
- Researchers use a written script to orally consent participants. Where appropriate, researchers share a print copy of a written consent script with participants.
- Researchers electronically display a written script (e.g., participant information form) for participants to view and/or affirm electronically.
- When applicable, researchers share more detailed information about participation—e.g., study background, etc., especially if a research study uses deception. In such cases where researchers use deception, a participant debriefing protocol can be required.

Ideals: Capacity to Consent, Freedom from Coercion, and Risks/Benefits

Closely related to voluntary consent—close extensions of the principles of voluntary consent to participate in research—are ideals of capacity to consent, freedom from coercion to consent, and assessment of the risks and benefits to participation. An early principle and clear focus on both the *Nuremberg Code* and *Declaration of Helsinki*, the idea that individuals cannot be forced to participate in a research study. Indeed, the very first sentence in the *Nuremberg Code*, after the voluntary-consent-as-absolute principle, states in certain terms that participation must be “without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion” and that participants “should have legal capacity to give consent” and (NIH, n.d.). When a participant does not have the capacity to consent, the *Declaration of Helsinki* specifies what to do: researchers must obtain content from a legally authorized representative (LAR), only if a study meets the following conditions:

- likely benefits participants who do not have the capacity to consent unless the study’s focus is on promoting the group associated with the individuals who are incapable of consenting;
- only if the condition that does not give participants the capacity to consent is “a necessary characteristic of the research group” (WMA, 2013);
- cannot otherwise include participants who have the capacity to consent; and
- involves only minimal risk to participants.

Clearly, the guidelines here move researchers to develop a protocol that protects folks who do not have the capacity to consent. For more information on legally authorized representatives, see Chapter 5 and Chapter 6.

One of the 10 principles in the *Nuremberg Code* relates to researcher assessment of risks and benefits for participants. In fact, the statement reads: “The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment” (NIH, n.d.). The *Declaration of Helsinki* reinforces this idea with a strong statement that “[m]edical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects” (WMA, 2013). Cautioning researchers to monitor risks associated with participation, the *Declaration of Helsinki* not only outlines a general ethical principle but also guides researchers about how to proceed with assessing risks and benefits in a study: “All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation” (WMA, 2013).

I discuss these issues in the context of research protocols, including consent procedures and assessment of risk-benefits, later in the book (in Chapter 6).

While you can see obvious risks, and clear harm, to research participants in historical abuses in biomedical experimentation, we see more recent clinical trials and social/behavioral science studies of potential risk to participants associated with research procedures. In some cases, the harm to participants outweighed the benefits to both participants and society, while in other cases clear violations of participant rights were documented. For example, a National Institute of Mental Health (NIMH) investigation into a \$3.1 million grant funded at the University of Illinois at Chicago found that Mani Pavuluri, a child psychiatrist and tenured professor at the university, conducted a study with “serious and ongoing noncompliance” of IRB principles (Cohen, 2018). Pavuluri’s study examined the effects of treatment with lithium on the brains of adolescents with bipolar disorder—using imaging during a manic state and after eight weeks of treatment. However, over 2009–2013 study period, the NIMH investigation revealed that Pavuluri violated terms of the funded grant by using lithium on minor children under the age of 13—lithium is not FDA approved for children under 12 years of age. In one of the most egregious findings—where research participants were put in direct harm—the investigation asserted that Pavuluri did not conduct required pregnancy tests on some of the adolescent girls enrolled in the study and did not appropriately apprise parents of adolescents of the risks of research participation. Finally, the investigation alleged that Pavuluri falsified research data to hide misconduct during the study. Institutionally, the NIMH investigation found that the University of Illinois at Chicago failed to sufficiently review Pavuluri’s initial submission to IRB—without a research protocol—and expedited the review without sufficient documentation. The university conducted an internal investigation and subsequently took action against Pavuluri: reviewing her clinical practice, barring her from conducting further research, and directing her to retract empirical research journal articles associated with three studies from the funded study.

Human Research Participants in US Clinical Trials: From Tuskegee to Terre Haute to Guatemala

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Whereas the *Nuremberg Code* and *Declaration of Helsinki* responded to abuses by medical researchers in the late 1940s through the mid-1960s—in Germany, Japan, and elsewhere—a US regulatory framework for research and a system of research governance developed in the 1970s. While legal and regulatory action emerged in the late 20th century in the United States, abhorrent abuses and horrifying mistreatment of humans in biomedical experiments could be seen in research work dating back to the early 1900s. Indeed, an early case where a US researcher led a biomedical experiment, known as the Bilibid Prison Vaccine Trials, that

resulted in the deaths of research participants occurred in Bilibid Prison in Manila, Philippines. In 1906, Richard Pearson Strong, then a professor in what is now the Harvard T. H. Chan School of Public Health, headed the Philippine Biological Laboratory and managed an investigation into cholera where 24 prisoners, 13 of whom later died, at Bilibid Prison were infected with plague organisms—without their consent. While the US Senate requested information on event, no formal or official US investigation followed, and the Philippine government’s response ended with no action—even though a local Philippine committee investigated and concluded that the deaths had been the results of Pearson’s negligence.

In another more well-documented and far-reaching case carried out by US researchers, the Tuskegee Syphilis Study led to the adoption of a systematic approach to research governance and national standards of research protections involving human participants. Between 1932 and 1972, over the course of the unbelievable 40-year experimental period, researchers with the Tuskegee Syphilis Study, or the United States Public Health Services Study of Untreated Syphilis in Black Males, enrolled 622 African American men in the study. As the title of the study implies, researchers designed experimental conditions to examine the natural course and treatment schedule of syphilis in African Americans over time. Recruiting generally low-income, rural African American men in the agricultural sector from Macon County, Alabama, officials from the US Public Health Service and Tuskegee University, a Historically Black College and University (HBCU)—along with community-based organizations in the African-American community—coordinated early and ongoing work in the study. Tuskegee and the community-based organizations in the African American community in Macon County supported, and collaborated in, the study under the belief that there were public health benefits. With incentives that included free medical care and meals, among others, researchers enrolled 431 participants who had contracted syphilis prior to the start of the study and 169 who did not have syphilis. During the study, researchers used more toxic, less effective treatments on syphilis-positive participants and did not treat these participants with penicillin, which had been approved—in 1947—as an effective treatment for syphilis and was being used in clinical settings to effectively control the disease. While funding for the project eventually ended, researchers informally continued the study until 1972, after a series of members of the biomedical and public health communities spoke out about the egregious ethical violations and maltreatment of participants. The study devastated many lives, leading to 28 participants who succumbed to the disease and 100 participants who died from complications of syphilis. In addition, the wives of 40 participants contracted the diseases, and 19 children of study participants contracted congenital syphilis at birth.

At the same time of the Tuskegee Syphilis Study, in 1943, John C. Cutler—with the US Public Health Service, and later, in 1944, John F. Mahoney, with the US Food and Drug Administration, led experimental trials of prisoners at the US Penitentiary in Terre Haute, Indiana. While using disclosures and documenting consent, researchers enrolled and intentionally infected 241 prisoners with gonorrhea to examine the effects of prophylactic treatment on the disease. With offers of

\$100 cash payments, among other research incentives, researchers ended the study after observing that the method of infection—direct deposit into the penis of prisoners—could not reliably be used to examine experimental hypotheses.

The Terre Haute prison experiments led to another study on syphilis conducted by the US Public Health Service—this time in Guatemala. With the approval and coordination of the Guatemalan government and funding from the US National Institutes of Health (NIH), US researchers designed and executed clinical experiments of soldiers, prisoners, sex workers, and mental health patients, to examine the effects of antibiotic (penicillin) treatment on syphilis and other sexually transmitted diseases. Between 1946 and 1948—and, in some cases, into the early 1950s—about 1,500 Guatemalans were enrolled in multiple tracks of the study, or more accurately, multiple clinical trials funded under the NIH grant. In the largest clinical trial, over 1,300 Guatemalans were intentional exposed to gonorrhea, syphilis, and chancroid. With intentional exposure by researchers directly injecting some individuals and a scheme where researchers paid infected sex workers to engage in unprotected intercourse with prisoners and others, just over half of the infected individuals received antibiotic treatment. In a similar trial, researchers designed experimental conditions to observe the transmission and prophylactic treatment of sexually transmitted diseases, including chancroid and gonorrhea. Ultimately, 83 Guatemalans succumbed to the diseases with which researchers infected them and died.

Following growing concern in medical, public health, and research communities and the public outcry over a series of atrocious, dehumanizing biomedical experiments—with a particular focus on the Tuskegee Syphilis Study—congressional members and officials in the Nixon Administration worked to pass the National Research Act in 1974. The law created, in Title II, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research—which convened from 1974 to 1978 with the express charge of outlining ethical principles in the conduct of human research and developing a US regulatory framework for the protection of human research participants, particularly in biomedical and behavioral science experiments. As a culminating event, the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the *Belmont Report*, a seminal artifact in the regulation of human participant research and system of research governance in place today. The far-reaching effects the *Belmont Report* (1978) can be seen in the adoption of Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46)—the Common Rule—which regulates the work that IRBs, researchers, and agency officials do in their human participant research roles.

Where US Regulations Start: The Belmont Report

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In a postwar era marked by patent violations of basic rights of human research participants associated with abuses in clinical trials sponsored and/or executed by

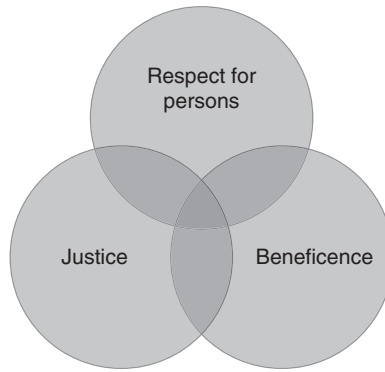
US government agencies and other public and private institutions, increasing attention from the public and research communities and a growing consensus in Congress to address ethical conduct in biomedical experiments, particularly with the Tuskegee Syphilis Study, led to the passage of the National Research Act and authorizing Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The commission's work focused on establishing a set of rules related to major concerns that emerged from questions about how human research participants had been mistreated in biomedical experimentation, including acceptable types of research and practice in the medical field, participant recruitment and inclusion/eligibility criteria for research participation, research with vulnerable groups, participant consent procedures, and assessment of risks and benefits of research participation. Between its convening years, 1974 and 1978, the commission issued multiple reports with regulatory recommendations, including research on fetuses, prisoners, and children and a system of research governance in IRB. The work of the commission has had lasting effects on what researchers do in practice—from protocol approval in the research process to specific procedures for participant recruitment and consent, data collection procedures with participants, and management, storage, and disposition of participant research data.

Another product of the commission that substantively changed the way that researchers conduct human research participant studies, the *Belmont Report*, articulated basic principles that undergird a regulatory system of research oversight and institutional systems of research governance and rules that guide a standard set of procedures with human participants. Near the end of its work, in 1978, the commission issued the *Belmont Report*, or the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*. Unlike previous reports that the commission issued, the *Belmont Report* offered a novel approach: accept the report and adopt the report's recommendations writ large—in their entirety.

Three Ethical Principles: Respect for Persons, Beneficence, and Justice

Perhaps no more far-reaching principles of ethical research conduct can be seen in the *Belmont Report* than respect for persons, beneficence, and justice. Indeed, these three principles—so closely tied to the report and developed as a response to prevent abuses seen in the Tuskegee Syphilis Study—are the most identifiable in practice and most meaningful as a guide to IRB reviewers and researchers. Both conceptually and in practice, these ideas extend a research focus from individuals to society: respect for persons (individual agency), beneficence (individual benefits), beneficence (broad benefits) and justice (fair distribution of benefits) (Figure 1.2).

Figure 1.2 Ethical Principles from the *Belmont Report*



Respect for Persons

The notion of respect for persons means that individuals have autonomy, or agency, and independence—that they must freely agree to participate voluntarily in a study and cannot be compelled or be subjected to a research procedure or procedures by coercion, force, or deception (with exceptions for deception in some experimental conditions). This is the idea that individuals have control over what they do and have a say in what happens (Anderson & Corneli, 2018). Here, the leading application of respect for persons is in the consent process—with consent documented as voluntary and participant agreement in writing that a participant freely and willingly accepts an invitation to engage in research activities (King, Henderson, & Stein, 1999). But documenting consent in written form, or any form, may not always be possible—and how you consent a participant may vary from case to case and by context.

As a central value in respecting persons, a focus on human dignity—inherent, absolute, and universal, where all people have worth and value as a member of the human family—undergirds consenting participants. Even in communities where communal consultation occurs or families consent to activities of individuals, the idea that individuals must agree to participate free from force or coercion is essential to upholding the dignity of humans. In some cases, researchers may compromise the idea of respecting persons when they work to obtain community consent *in place of* individual consent or when they waive written informed consent or any consent at all. For example, in placebo-controlled clinical research, where experimental designs may drive decisions about waiver of consent and “surrogate consent” (Kraybill & Bauer, 1999, p. 195), research practice runs counter to this principle and researchers evade participant rights to self-determination.

Integral to the idea of respect for persons in consenting is the capacity to consent, where researchers consider individual capabilities to assess participation in procedures and agree to engage in research activities. With capacity, we generally refer to age—age of majority as an adult or minor child under the age of 18 years—impairment in decision-making, life circumstance, and socioeconomic or educational status. Using regulatory rules outlined in the Common Rule (see below under “The Common Rule: What 45 Code of Federal Regulations Part 46 Means for You as a Researcher”), we can see that groups of individuals where capacity to consent must be considered include children, individuals who are incarcerated (prisoners), and individuals with impaired decision-making capacity or who are economically or educationally disadvantaged. As groups that have experienced particular abuses in human experimentation in the past, they are considered to be especially vulnerable—so researchers have to take specific precautions and procedures that account for unique capacities to consent. Here, using a legal representative to consent in the case of minor children or individuals with impaired decision-making may be required to protect prospective participants. More on consent procedures with vulnerable groups in Chapter 6!

A final implication for research practice of respecting persons relates to “spatial and informational privacy” of participants (King, Henderson, & Stein, 1999, p. 25). Here, researchers need to develop measures to protect the physical space that individuals have as a function of their personhood—which relates to the idea of autonomy and self-determination. In addition, the individual right to privacy of personal information needs to be protected—from before initial contact, if applicable, to after data collection, analysis, and dissemination ends with the storage and maintenance of study records.

Beneficence

The idea of beneficence requires researchers not only to “do no harm,” as a practice in biomedical clinical settings, but to also ensure that research work is done with the utmost care and concern for the wellbeing of participants so that risk of injury or death to participants does not increase. What is more, this latter concepts of avoiding or limiting risk to participants—physical, psychological, social, legal, economic, etc.—intersects with a need to maximize potential benefits to participants, compelling researchers to consider design, methods, and procedures or activities in which individuals participate so that they will likely have some sort of personal benefit. These two ideas—“duty to do good” and limit risk/promote benefits (King, Henderson, & Stein, 1999, pp. 8–9)—focus on the people with whom we work in the field. Like consent procedures, considering how our research work impacts folks in the field or the lab forces us as researchers to do more than contribute to scholarly knowledge and clinical practice. As we conceptualize an investigation, this idea means that we shape procedures—research activities in

which we plan to ask participants to engage—to limit pain or hurt in any way and facilitate some sort of good for participants.

Does beneficence mean, in practice, that we cannot use procedures that may cause harm? No, not at all—from biomedical clinical trials of new drugs to promising practices in behavioral therapies, many research procedures, in experimental and observational designs, may produce pain across the spectrum. Therapeutic remedies require experimentation with the human body and behavioral interventions may elicit mild mental trauma—but the thrust of these activities leans toward doing good in the research setting and society and associates with potential benefits to individual participants. In some cases, particularly in biomedical research, the idea of beneficence may be subject to broad interpretation where researchers look beyond individual benefits and more toward benefits to the field of medicine and advances in treatment of disease (Kraybill & Bauer, 1999). But, as Kraybill and Bauer argue, it is specifically in the biomedical field that the practice of “do not harm” needs to be upheld.

Justice

The principle of justice refers to the idea that benefits from the study be fairly and equally distributed among prospective research participants and the groups and communities from which they are recruited. Originally conceptualized as “a principle designed to eliminate biases against groups of people” (King, Henderson, & Stein, 1999, p. 9), justice has generally been applied to research work in sampling, recruitment, and selection of folks who will likely benefit from participation in research activities and findings of research investigations. That is, justice is a principle of the equitable inclusion in research studies and distribution of benefits across groups that may stand to gain from research results. Accordingly, developing inclusion criteria that will likely result in the equitable selection of folks based on race/ethnicity, gender, language, sexuality, geography, and community—among others—advances the idea of justice in research practice.

Historically, researchers from white male European and US middle-/upper-class backgrounds tended to recruit folks who looked like, lived close to, and behaved similarly to them. As the biomedical, health, social, and behavioral science fields developed, researcher may have generally included measures to promote justice in research designs—but normative research structures and procedural standards frequently built in bias against women and people of color have been observed. But even as some researchers have worked to apply approaches for equitable recruitment and selection of participants, the issue of power relationships and hierarchies (King, Henderson, & Stein, 1999, p. 9) between researchers and participants from communities of color and historically marginalized groups has not been at the forefront of considerations in conceptual and procedural approaches in research. Working to address not just historical biases in research but broader applications of recruitment, selection, and benefits

to research participants, researchers have moved to use specific forms of inquiry like participatory action research (PAR) and community-engaged research (CEnR), for example, to promote culturally-responsive liberation and empowerment among family, groups, and communities that have been traumatized by systems of oppression for far too long.

A final consideration here is that the principle of justice as equitable distribution of benefits across groups in society can sometimes lead to an ends-means approach to procedures where recruitment of participants from low-income communities and communities of color that are underrepresented in research investigations may mean intentionally waiving informed consent or using surrogate consent in place of individual informed consent under the argument that people in low-income/low-socioeconomic/high-historically underserved communities deserve to benefit from research but are harder to reach (Kraybill & Bauer, 1999, p. 195). But this end-means approach is problematic and must be reviewed by an IRB before procedures can be used in the field.

In Focus in *Your Study*: The *Belmont Report's* Ethical Principles of Respect for Persons and Justice

Thinking critically about local cultural norms and beliefs of a group or groups of research participants, what does respect for persons mean for you in the context of your study or studies?

What about justice? How do you or will you structure your study to ensure a fair and equal distribution of risks and benefits to prospective research participants?

As principles that lead researchers as guides in work with human research participants, beneficence has emerged as central to assuring the overall health and safety of individuals who engage in research activities—reducing risk, decreasing harm, and increasing benefits to individuals. Taken together, Shamoo and Resnik (2009) argue that respect for persons and beneficence allows us as researchers to “use humans in our research provided that we take steps to promote and respect their inherent moral worth” (p. 218). To be sure, the principles in the *Belmont Report* undergird both ethical guidelines and a regulatory framework that governs research review in human participant contexts—but these principles, in many cases, do not have the force of legal statutes, regulatory rules, and/or institutional policies. While they undergird how we review and approve research protocols in IRB contexts and may be in the forefront of researchers’ work with participants,

they require just an extension into areas of regulation to effect substantive change. Even then, regulations may not be enough to safeguard human participants in all research contexts.

The Common Rule: What 45 Code of Federal Regulations Part 46 Means for You as a Researcher

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Decoding the Common Rule—or 45 CFR 46

What's meant by 45 CFR 46? Maybe it's a bit arcane or a little esoteric, but it's worth noting that federal regulations—also known as administrative law—that are associated with executive branch departments and agencies of the US government include locational information, including a title, or general category, and subpart or specific section. In the Common Rule's case, "45" refers to the regulatory title—public welfare. "CFR" is a shorthand abbreviation for Code of Federal Regulations,

which have the force of law. And the meaning behind "46" is a bit trickier to get to—mostly because there are a few bureaucratic layers hidden in the subpart. To arrive at part 46, first go to "Subtitle A—Department of Health and Human Services" and "Subchapter A—General Administration," then search for "Part 46—Protection of Human Subjects." Of course, within Part 46, there are five subparts—and it is in these subparts where you can find the regulations!

In extending effects of the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and developing a system to apply principles of the *Belmont Report*, the Office for the Human Research Protections (OHRP), in the US Department of Health and Human Services, under the authority of the National Research Act, issued Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46)—or the Common Rule—in 1981. With a wide reach to the work of researchers—across public and private institutions, federal to state agencies, colleges and universities, and commercial entities—the Common Rule touches what most of us do in research practice. You can see in Box titled "The 'Common' in the Common Rule: Regulatory Application in the Federal Bureaucracy" that 45 CFR 46 extends to a long list of federal agencies or departments, which have agreed to follow Common Rule regulations. While the US Department of Health and Human Services houses OHRP—with central oversight authority of Common Rule regulations—and the Food and Drug Administration (FDA)—with regulatory authority in biomedical experiments—many federal departments and agencies in the executive branch use these regulations to govern research review.

The “Common” in the Common Rule: Regulatory Application in the Federal Bureaucracy

As the Common Rule, 45 CFR Part 46, regulations extend to multiple federal agencies, including:

- 7 CFR Part 1c - Department of Agriculture
- 10 CFR Part 745 - Department of Energy
- 14 CFR Part 1230 - National Aeronautics and Space Administration
- 15 CFR Part 27 - Department of Commerce - National Institute of Standards and Technology
- 16 CFR Part 1028 - Consumer Product Safety Commission
- 22 CFR Part 225 - Agency for International Development (USAID)
- 24 CFR Part 60 - Department of Housing and Urban Development
- 28 CFR Part 46 - Department of Justice - National Institute of Justice
- 32 CFR Part 219 - Department of Defense
- 34 CFR Part 97 - Department of Education
- 38 CFR Part 16 - Department of Veterans Affairs - Office of Research Oversight - Office of Research and Development
- 40 CFR Part 26 - Environmental Protection Agency - Research and Development

- 45 CFR Part 46 - Department of Health and Human Services
- 45 CFR Part 690 - National Science Foundation
- 49 CFR Part 11 - Department of Transportation

In addition, three departments and/or agencies comply with all subparts of 45 CFR Part 46, even though they have not issued the Common Rule as regulations:

- The Central Intelligence Agency, by executive order, must comply with all subparts of 45 CFR Part 46. (Executive Order 12333, paragraph 2.10)
- The Department of Homeland Security, created after issuance of the Common Rule, has chosen to apply all subparts of 45 CFR Part 46 to its human research activities. (6 U.S.C. section 112)
- The Social Security Administration was separated from HHS in 1994 and absent action by the administrator, must apply all regulations that applied to SSA before the separation. (42 U.S.C. section 901) (<http://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html>)

The Common Rule starts with very basic working definitions of research that is subject to research governance under IRB systems. What does research mean in this context? When does research with humans need to be reviewed? Here’s what the regulations say:

Research means a **systematic investigation**, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Human subject means a **living individual** about whom an investigator (whether professional or student) conducting research obtains: **data through intervention or interaction with the individual or identifiable private information.**

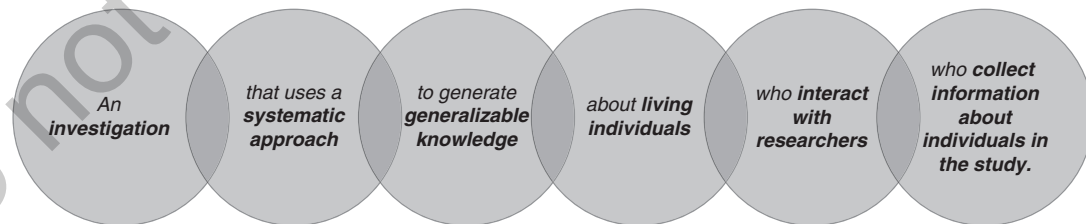
(Office for Human Research Protections, 2018c)

Updates to the Common Rule implemented in 2018 (i.e., 2018 Requirements) further define what researchers collect from human research participants, including when a researcher “[o]btains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or [o]btains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens” (Office for Human Research Protections, 2018d) (Figure 1.3).

As you can see, the Common Rule clearly delineates what research means—an **investigation** that uses a **systematic approach**, results in **knowledge** that can be **generalized**, and involves **people who are alive and enrolled in an activity or interact with researchers who collect information about them**. But what types of research activities do Common Rule regulations exclude? You can see a clear delineation of categories of research work that are not subject to policies to protect human research participants, including scholarship about a specific individual or group of individuals—like biographical or historical accounts or stories—and the collection of personally identifiable information and/or biospecimens related to public health monitoring, criminal justice administration, or “operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions” (Office for Human Research Protections, 2018d).

While defining human subject research or research with human participants, regulations outline what an investigator is. In this way, the Common Rule includes both parties to an investigation and clarifies how researchers and research

Figure 1.3 The Common Rule’s Definition of Human Subjects Research



participants are subject to regulatory oversight. To this end, 45 CFR 46 uses the term “investigator” as follows: “an individual performing various tasks related to the conduct of human subjects research activities, such as obtaining informed consent from subjects, interacting with subjects, and communicating with the IRB” (OHRP, 2019). Using tasks as defining characteristics, regulations outline what investigators do in research projects—they interact with and gather information from research participants.

Beyond initial working definitions of *what* and *who* falls under regulatory oversight of human participant—or human subjects—research, the Common Rule defines and outlines a centerpiece of protections for individuals involved in studies: a system of research governance. Here, you can see what informs the protocol approval process through which your proposed research projects undergo review. Known widely as IRB, institutional review boards implement Common Rule regulations in institutions and organizations across the country, including “any public or private entity, or department or agency (including federal, state, and other agencies)” (Office for Human Research Protections, 2018d). Ultimately, all research that involves human research participants covered under Common Rule regulations must be approved by an institutional review board—where a “determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements” (Office for Human Research Protections, 2018d).

What else is in the Common Rule? Both the Pre-2018 Requirement and 2018 Requirements include five parts as follows:

- Subpart A—Basic HHS Policy for Protection of Human Research Subjects
- Subpart B—Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- Subpart C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D—Additional Protections for Children Involved as Subjects in Research
- Subpart E—Registration of Institutional Review Boards (Office for Human Research Protections, 2018c; 2018d)

You can see from a quick glance at 45 CFR 46 that two of the five subparts relate directly to IRBs—from basic definitions and review procedures to requirements for registration. The majority of the parts of the Common Rule relate less to administrative or logistical issues and directly to protections of vulnerable groups, including women, fetuses, and neonates; prisoners; and children. More on working with vulnerable groups in Chapter 6!

IRB Review: Federal Policy and General Principles

As you can see from Pavuluri's case, discussed earlier in the chapter, when researchers fail to comply with basic principles of human participant research articulated in the Common Rule, they are subject to regulatory investigation and administrative and/or criminal action. As egregious as the Pavuluri case is, another recent case highlights the need for federal oversight of research governance and a system of research review in clinical and campus settings. Indeed, the work that William Halford did as a professor at Southern Illinois University (SIU) has led to a criminal investigation by the Food and Drug Administration (FDA). Both in 2013 in hotel rooms in Illinois and in 2016 in St. Kitts and Nevis, Halford oversaw experimental herpes vaccine injections with human research participants (Taylor, 2018). Why a criminal investigation? In this case, Halford—now deceased—was an SIU professor and acted in a medical capacity by overseeing injections without appropriate medical training or licensure as a physician at the time of the vaccine trials. What is more, the investigation focused on whether the trials evaded and/or avoided regulatory-compliant IRB protocol approval and proper authorization/oversight from the FDA. Certainly, issues of informed consent and experimental research participants' bill of rights, concerns for patient health and safety, and lack of thorough assessment of risks and benefits in the study could all form areas of focus for regulatory and/or criminal investigations.

In a separate experimental trial designed at Harvard University, funded by the NIH, the CLOVERS (Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis) study is the subject of a complaint filed by Public Citizen (Harris, 2018). In a letter sent directly to OHRP's director, the director and founder/senior advisor of Public Citizen's Health Research Group request that OHRP stop the CLOVERS study—including halting enrollment of human research participants and—and initiate a compliance oversight investigation. What does the letter allege in the complaint? Focusing on the study's experimental design, experimental procedures, and consent procedures, the letter argues that (a) without a control group but with two experimental or intervention groups, (b) without considering variations in current standards of care based on the severity of sepsis, and (c) without detailed and reasonable risks associated with study procedures, the CLOVERS study unnecessarily puts participants at health risk and may not be able to draw conclusions that improve standards of care (Public Citizen, 2018). For their part, CLOVERS study principal investigators maintain that the study has undergone regulatory approval and is compliant with current standards of research practice—with one of the principal investigators stating: "The study protocol was designed by expert clinicians in emergency and critical care medicine representing nearly 50 hospitals in the United States and follows a well-accepted design" (Harris, 2018).

What is IRB and what does IRB do in implementing Common Rule regulations? The most basic definition can be seen in the regulations themselves: "an institutional review board established in accord with and for the purposes expressed in this policy" (Office for Human Research Protections, 2018c; 2018d). Aside from being

overly general and a bit amorphous, the definition is also somewhat circular—like saying an IRB is an IRB because an IRB looks and acts like an IRB. Well, fine, this definition works well if—perhaps—you are a campus compliance officer or IRB committee member who works regularly or has advanced training with human research participant protections and research governance. For the rest of us, just what is an institutional review board and what do they do? There’s more in the regulations that meaningfully help us see what IRB does: they approve research plans so that what researchers do complies with protections of human subjects.

Looking more closely at what IRBs look like and what IRBs do, the Common Rule specifies four major areas of operation as follow:

- An institution must maintain and publish membership for an IRB (as a regulatory function) with **a minimum of five committee members from diverse cultural, racial/ethnic, and gender backgrounds**, and IRB membership has to include at least one member who is not affiliated with the institution and one member each from a “scientific” field and “nonscientific” field (Office for Human Research Protections, 2018d), although these fields tend to be socially constructed categories of science (i.e., using a positivist lens of “scientific” to refer to life and physical science disciplines, while “nonscientific” generally means social and behavioral science disciplines).
- Aside from institutional support for meeting space and staff resources, **IRBs must develop and use written procedures for research protocol review and approval**—including quorum for committee review—protocol approval modifications (i.e., changes to approved protocols), more-than-annual review of protocols, adverse events, and protocol approval suspension or termination.
- As part of review and approval of procedures, **IRBs have to specify what researchers include in informed consent forms/procedures** to document or waive documentation of consent with in-person and virtual (remote data collection—an issue in focus during/after the COVID-19 pandemic in 2020) and share, in writing, requirements for initial and continuing review of protocols and outcomes of IRB review—including IRB determination for protocols not required to be reviewed annually under continuing review (i.e., protocols eligible for expedited review or approved protocols in the analytical phase of research).
- **IRB records must be maintained for three years—and three years from the completion of IRB-approved research protocols**—including research protocols reviewed by IRBs, minutes of IRB committee meetings, documentation of IRB determinations/outcomes of research protocols, and responsibilities of an institution and IRB committee, respectively.

You can see here that, while the Common Rule describes quite a bit about IRBs, the regulations ask campuses to do a lot of work to fill in what is more of a detailed outline—with the expectation, and really requirement, to establish local policies and procedures associated with the implementation of human research participant protections in the Common Rule. More on local campus policies below as this chapter unfolds and throughout the book and in Chapter 3, specifically!

Recent Updates to the Common Rule: Major (and Minor) Changes to the Research Governance Process

When you consider the historical events that led to a regulatory rules and system of research governance in the United States, you can see why a basic framework for ethical treatment of human research participants was, and still is, necessary. But what has happened since the National Research Act authorized the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to issue the *Belmont Report*, ushering in the Common Rule? Several decades and multiple revisions later, the Common Rule recently underwent a major update in 2017.

Now known as Pre-2018 Requirements—original and revised regulatory text prior to the most recent revisions—and 2018 Requirements, Common Rule revisions effective January 21, 2019 include the following major and minor updates.

- **Revising existing exempt research categories and creating new exempt research categories**, expanding from six (Pre-2018 Requirements) to eight the number of exempt categories and amending multiples existing categories. One existing exempt research category left unchanged by the 2018 Requirements includes taste and food quality evaluation and consumer acceptance studies. Exempt categories (i.e., research now reviewed in exempt categories) changed by 2018 Requirements include (a) educational research that does not adversely impact instructional time or student learning (i.e., if research activities significantly interrupt instruction, then exemption would not apply); (b) interactions (not interventions) that involve educational testing, surveys, interviews, or observations that do not put participants at criminal, civil, or financial risk and information is collected without identifiable data or, if identifiable data are collected, a limited IRB review is done; (c) secondary research that involves publicly available HIPAA-regulated identifiable research data or biospecimens that are not reidentified and the researcher does not contact research participants after data collection ends; and (d) federal agency demonstration projects conducted directly by or funded by a federal agency to evaluate and improve programs. Finally, three new exempt research categories associated with the 2018 Requirements include (a) behavioral

interventions with adult research participants that do not put participants at criminal, civil, or financial risk and information is collected without identifiable data or, if identifiable data are collected, a limited IRB review is done; (b) storage and maintenance of broad-consented identifiable research data or biospecimens; and (c) secondary research of broad-consented identifiable research data or biospecimens. More on exempt research categories in Chapter 4 and Chapter 5!

- **Updating groups of vulnerable research participants**, including children, individuals who are imprisoned, and individuals with impaired decision-making capacity or who are economically or educationally disadvantaged. While rule changes technically exclude pregnant women, fetuses, neonates, individuals who are elderly, and individuals who are victims of crime or abuse, care still needs to be taken with these groups and special accommodation and/or protections may need to be used.
- **Presenting research participants with essential information in consent procedures** at the top of a consent form and/or start of a consent process. This information includes a note that what a researcher requests is participant consent, study purpose, type of involvement and time commitment, risks and benefits of participations, and alternatives to participation. And now, in a post-COVID-19 pandemic world where virtual/remote data collection is normative, IRBs issue guidance on consenting with remote data collection.
- **Allowing for broad consent for storage, maintenance, and use of identifiable research data** in the future with participants in a current study. For researchers, broad consent must include the following with research participants: (a) asking for consent of identifiable research data for future use; (b) notifying if/when identifiable research data will be used and, if applicable, clinically relevant research results in future studies will be shared; (c) listing research studies where identifiable research data may be used in the future; (d) referring to researchers with whom and institutions where identifiable research data may be shared; and (e) including time periods where study records will be stored.
- **Requiring research protocols where cooperative or multi-institutional investigations to use a single IRB for protocol approval.** With an effective date of January 20, 2020 (or later), this new rule includes an exception under two conditions with protocol approval from more than one institution where (a) the law requires protocol approval by more than one institution and (b) where a federal agency or department necessitates protocol approval by more than one institution.

- Doing away with the practice of IRB review of extramurally funded, sponsored grant applications/proposals connected to the research protocols.

The Common Rule in Practice Today: Observations on a Regulatory System of Research Governance

Between the *Belmont Report* and Common Rule, researchers in the United States have worked within a regulatory system guided by principles that promote the idea of self-worth, individual right of self-determination, and freedom to choose how to respond to a request to participate in research. Informed by the *Nuremberg Code* and *Declaration of Helsinki*, the *Belmont Report* codified what have been seen as universal ethical principles. Autonomy, agency, individualism—these ideas are essential to the guiding values in a system intended to protect human research participants—particularly from abuse by researchers who may see exigencies in clinical trials or field research over needs or rights of individuals who participate in research activities. But while many researchers see a system of regulatory protections, others see what King, Henderson, and Stein (1999) discuss as Western moral imperialism or principalism in international contexts (p. 12). They go on to say that “holding researchers in developing countries to irrelevant and impossible-to-meet standards” (p. 12), where folks in cultural groups and communities outside the West reproduce as normative more communal and familial forms of decision-making.

A Western imperialist pattern of promoting and/or codifying moral principles in international contexts that guide/govern human research participant decisions are important to note—as they tend to follow broader patterns of colonization by the United States and European states. Where knowledge and cultural systems have been destroyed and entire groups of people have been subject to genocide, dispossession of land, and persistent or residual trauma—using a system of knowledge and cultural values related to Western philosophical thought to decisions about how to invite and recruit individuals may extend a colonial system of oppression and do harm to folks who have suffered under such systems. Challenging this approach, some researchers have argued what King, Henderson, and Stein (1999) discuss as system to regulate research from a relationship standpoint—using local contexts and relationships between folks to guide decision-making about research participation. The key question here is, how do folks relate to each other in their families, communities, places of work, etc.? What are local beliefs, customs, rituals, and values—and how do they relate to interests/needs in a research study?

Even in local contexts with a culturally sensitive approach to a research project where researchers need to account for local traditions, customs, and systems of knowing and relating, individuals and, in particular, vulnerable groups like women, children, prisoners, and minoritized groups, and individuals or groups with impaired decision-making capacities may be mistreated and/or abused when a research opportunity presents financial gain or self-gain in some way. Perhaps a balance between individual rights of research participants, characterized by Western value systems and embedded in human research participant regulations, and culturally-sensitive approaches of researchers may best work to protect people who sign up for a study.

Beyond implications for moral imperialism of Western values and reproduction of colonizing research patterns, some wonder if the system of research review and governance has overreached. As Klitzman (2015) observed, IRBs wield a lot of power—the power to approve or stop investigations that involve human research participants. Indeed, Klitzman reported that “[r]esearchers complain of IRB overreach, delays, and adversarial stances (p. 241)—whereas IRB committee members often differ in their view of research governance work, generally feeling “good about their work and that they have relatively little power” (p. 241). King (2010) notes that “ethical debates among social scientists did not greatly shape subsequent regulations, which were devised by medical and psychological researchers and ethicists who knew and cared little about the work of social scientists” (p. 10), which may explain some of the animosity toward IRB protocol review that researchers across the board and researcher from social scientists feel. Schrag (2010) sheds light on how the outcome of the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the *Belmont Report* and Common Rule regulations. Here, Schrag notes:

Though the history of IRB review of the social sciences spans more than forty years, two years—1979 and 1980—stand out as the only period in which social scientists played a significant role in shaping federal and university policies toward their research. The skirmishes at Berkeley and Colorado, the angry letters to the National Commission, and the testimony at the 1977 hearings expanded into a larger national movement bringing together hundreds of scholars. These scholars united behind a single proposal and supported it with essays in the scholarly and popular press and with more subtle lobbying in the executive and legislative branches of the federal government. For a while it seemed as though they would get everything they wanted, and when new regulations were issued in January 1981, they included significant concessions. But social scientists failed to get their preferred language encoded in legislation or in regulations, with severe consequences for future researchers.

(p. 96)

From a social science perspective, rules conceptualized and crafted by biomedical and behavioral researchers as a response to abuses committed largely by biomedical researchers may be seen as a bit strange. For example, during fieldwork, what would a social scientist do with an experimental subjects bill of rights? Deception? Usually not a part of naturalistic inquiry. What about physical harm? While considerations for risk and benefits need and must be part of all human research participant research—irrespective of academic training and disciplinary affiliation—a central focus of the regulatory framework has been on limiting, reducing, and mitigating physical (and psychological) harm. To this point, Schneider (2015) notes:

Research is safer than regulationist rhetoric implies. Social-science research search and much biomedical research cannot harm subjects physically. Most other research involves little opportunity for physical harm, serious physical harm is improbable in most of the remaining kinds, and many serious risks are diminished by the structure of research. And while all research can inflict social, psychological, and dignitary harm, it happens little and is rarely grave.

(Kindle Locations 207–209)

Whereas research may be safer in social science contexts—at least in physically invasive terms—there still exists a risk, even if small, to individuals who participate in research activities. With three broad core principles that inform the Common Rule—respect for persons, beneficence, and justice—regulations may not be enough to protect all groups. That is, regulations tend to be a bit general and lack specific details to apply uniquely to all individuals; they simply do not cover all circumstances at all times. To this point, Coleman, Menikoff, Goldner, and Parasidis, 2015 argue that “current regulations provide insufficient respect for persons and are not sufficiently responsive to the full array of vulnerability experienced by prospective participants” (Kindle Locations 4980–4981). They continue:

Providing protections for all potentially vulnerable groups would require developing an unwieldy list of additional subparts. To the extent that different groups may require the same types of protection, the addition of a long list of subparts may introduce unnecessary duplication in the regulations. A group-based approach to vulnerability leaves unanswered questions about how to safeguard persons with multiple vulnerabilities. The status of particular groups may change. For example, as members of a particular group become increasingly less subjected to stereotypes...

(Kindle Locations 4982–4987)

Between regulatory overreach and implementing regulations that address the specific needs of individual groups, research governance functions to extend protections of the Common Rule. More details on this process in the chapters to follow!

CHAPTER SUMMARY

This chapter contextualized what you do in the IRB review process, outlining historical events that led to the system of research governance that we see today. From an international perspective, you can see early protections of human research participants emerged as a response to atrocities committed in the mid-to-late 20th century in Germany and Japan. First codified in the *Nuremberg Code*, the *Declaration of Helsinki* extend principles of voluntary consent, albeit modified in the conditions of consent, and ideals of capacity to consent, freedom from coercion, and risks/benefits. As a self-governing system of protections of human participants in clinical research for the biomedical community, the *Declaration of Helsinki* informed the development of protections for research participants in the United States with the *Belmont Report* and later Common Rule. With the Common Rule, research governance in US biomedical and academic settings, in particular, took shape as IRBs and required researchers to submit proposed plans for participant recruitment and consent process, procedures with participants, risks and benefits to participants, and minimization of harm to participants, management and storage plans for research data, and qualifications of researcher(s). Recent changes to the Common Rule reflect changing needs of research communities, with updates to categories of review and consent procedures. How institutions review research protocols with these principles as guides may vary—for example, protocol submission systems, review schedules, designation of review boards by discipline, etc.—but institutions must comply with federal regulations articulated in 45 CFR 46 or the Common Rule. This is where students and faculty should access local policies and practices and work closely with their local campus IRB and compliance officer(s).

IMPLICATIONS FOR YOUR PROTOCOL: QUESTIONS TO ASK YOURSELF

1. Reflect on the specific safeguards for participants in your research project(s). How do historical patterns of abuse in human experimentation inform what you do to protect individuals who participate today?
2. Thinking more about participation safeguards, do community or group elders always know what is best for all members at all times? Does a hierarchy of power relations based on gender, ethnicity, sexuality, etc. serve all members of a family or group equitably? How do you account for these dynamics in your research?
3. What have you heard about IRB on your campus from folks with whom you work? What's the prevailing perception of the IRB process and value of

IRB review? How might this general climate about research governance affect you?

CONCEPTS IN FOCUS FOR YOUR IRB WORK

- Voluntary participation in human research, consent to participate in research, freedom from coercion to participate in research, and understanding risk/benefits to participation
- Principles of respect for persons, beneficence, and justice in human research participation
- Research governance and regulatory framework for human participant research in the United States

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