

PROPOSED REVISIONS TO THE COMMON RULE:
CAN IRBS REALLY ENHANCE PROTECTIONS
WHILE REDUCING BURDENS?

BY

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LIST OF ABBREVIATIONS

AAHRPP	Association for the Accreditation of Human Research Protection Programs
AAMC	Association of American Medical Colleges
ACHRE	Advisory Committee on Human Radiation Experiments
ANPRM	Advance Notice of Proposed Rulemaking
APA	Administrative Procedures Act
CFR	Code of Federal Regulation
CIOMS	Council for International Organizations of Medical Sciences
CIRCARE	Citizens for Responsible Care and Research
DHEW	Department of Health, Education and Welfare
DHHS	Department of Health and Human Services
EAB	Ethics Advisory Board
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
HEW	Department of Health, Education and Welfare
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
KKI	Kennedy Krieger Institute
LAR	Legally Authorized Representative
NBAC	National Bioethics Advisory Committee
NIH	National Institutes of Health
NPRM	Notice of Proposed Rulemaking
OHRP	Office of Human Research Protection
OIG	Office of the Inspector General
OPRR	Office for the Protection of Research Risks
PHS	Public Health Service
PRIM&R	Public Responsibility in Medicine and Research

SIIDR	Subcommittee for the Inclusion of Individuals with Impaired Decision-Making in Research
The National Commission	The National Commission for the Protection of Subjects of Biomedical and Behavioral Research
the Yellow Book	The Institutional Guide to DHEW Policy on Protection of Human Subjects
WMA	World Medical Association

ABSTRACT

Rosemary A. Juster

PROPOSED REVISIONS TO THE COMMON RULE: CAN IRBS REALLY ENHANCE PROTECTIONS WHILE REDUCING BURDENS?

Thesis under the direction of Nancy M. P. King, J.D.,
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On July 26, 2011, the Department of Health and Human Services (HHS) announced its intention to significantly revise and update HHS regulations regarding human subject research for the first time since 1991, when it originally promulgated what has become known as the Common Rule. HHS further solicited comments to its proposed revisions contained in this Advance Notice of Proposed Rulemaking (ANPRM) through the use of 74 questions. Over 1100 interested parties responded to these questions. HHS is still in the process of reviewing and analyzing the responses. No further action has been taken and, as of this writing, a formal Notice of Proposed Rulemaking (NPRM) has not been issued.

The stated goal of the ANPRM is enhancement of protections for human research subjects, with simultaneous improvement of the effectiveness of the federal oversight system. This thesis addresses certain of the proposed revisions, particularly those affecting Institutional Review Boards (IRBs) while also addressing certain comments from interested stakeholders in response to the ANPRM. While certain of the proposals may merit careful consideration and possible rule revision, I argue that many of the

proposed changes are already allowed under the current regulatory scheme. It is really OHRP guidance and better education that is needed, and not a major overhaul of the Common Rule.

I also address the long overlooked vulnerable population of decisionally impaired adults and propose additional protections for this group, consistent with the current regulations for protecting other vulnerable categories of research participants.

INTRODUCTION

The history of medical research is one of repeated instances of harm done to individuals while pursuing knowledge that is intended to increase the public's welfare. As Dr. Marcia Angell, former editor-in-chief of the *New England Journal of Medicine*, is frequently loosely quoted: “Ethical lapses are almost never cases of bad people, doing bad things, for no reason. Rather, they are good people, doing bad things, for good reasons.” (Sodeke 2005, quoting Angell).

There are many examples of good intentions leading to unimaginable, and irreparable, harm; including, for instance, a death related to gene transfer research gone awry or a healthy volunteer dying in an asthma study (Noah 2004). Exploitation of human subjects in research would seem to be borne out by numerous instances of “scandalous practices” (Mastroianni and Kahn 2001). Some of these practices include: lack of information for truly informed consent, exploitative subject recruitment, use of vulnerable populations, and exposure of subjects to significant risks without direct benefits (Id. at 22). It is this exploitation of human subjects in research that drove the development of protection policies in the U.S. (Id. at 21).

The recognition of early human subject research abuses also served as a basis for the bioethics movement. One of the fundamental questions of the bioethics movement, as articulated by Jay Katz in the Introduction to his book *Experimentation with Human Beings*, is “When may a society, actively or by acquiescence, expose some of its members to harm in order to seek benefits for them, for others, or for society as a

whole?” (Katz 1993). Katz goes on to explain that when he first raised the question it was only a “When” question and not “Whether” such experimentation was ever justified. As he acknowledges, it is “ultimately necessary to conduct human trials in order to acquire the necessary knowledge to alleviate human suffering” (Katz 1993, at 7).

Importantly, the subjects' rights in being secure in their person and body remain sacrosanct and must be respected in any human research endeavor. As the 18th century philosopher, John Locke, described the right to bodily integrity, he wrote, “every Man has Property in his own Person. This no body has any right to but himself” (Locke 1960). In numerous cases, beginning well over a century ago, our Supreme Court has articulated the right to bodily integrity, explicitly noting that such a right is fundamental to the common law: “No right is held more sacred, or is more carefully guarded, by the common law, than the right of every individual to the possession and control of his own person, free from all restraint or interference of others, unless by clear and unquestionable authority of law” *Union Pacific Ry. v. Botsford*, 141 U.S. 250 (1891).

Prior to the twentieth century, research ethics were primarily governed by individual conscience and professional codes of conduct. Whether and how human beings might be investigated, however, has always been subject to the laws and customs of the society and government of the time. For many reasons, some of which follow, the second half of the twentieth century saw the need for an elaborate set of rules and regulations about human subject research. It is the establishment of these regulations, and primarily their ethical underpinnings, which is the subject of this thesis. I focus on the development of

Institutional Review Boards (IRBs) as the nearly singular oversight structure for biomedical research, and seek to determine if this structure can adequately protect human subjects, and in particular, vulnerable populations. Chapter One provides historical context for the development of the federal regulations governing most human subject research and establishing IRBs, focusing on the reasons for the need for legal protections of human subjects involved in research. Chapter Two focuses on the role of IRBs and their effectiveness in affording protections while balancing scientific pursuits. Chapter Three discusses the 2011 proposed changes to the regulations that govern human subject research, particularly focusing on those that deal with or could impact IRBs. I question whether such significant changes to the current regulatory scheme are actually the most efficient way to achieve the stated goals. While some regulations may benefit from a revision or modernization as advocated, other situations may benefit from a review of the flexibility already in the regulations with additional, appropriate guidance and education. Chapter Four sets forth recommendations for consideration with respect the long-overlooked vulnerable population with decisional impairment, with a focus on additional guidance and education for IRBs in dealing with research endeavors involving this unique population. Chapter Five sums up the issues and provides my last thoughts and impressions on the ultimate effectiveness of the current regulations, the proposed changes to these regulations, and the IRB structure in general.

This thesis questions whether IRBs are the most efficient and effective oversight tool for ethically balancing both the protection of the human subjects and the furtherance of scientific pursuits. As Mastroianni and Kahn opined, the early focus in the development

of human subject protections in research was on protection from risks. Only later did the focus shift to a fair distribution of access to potential benefits of research (Matroiani and Kahn 2001, at 22). These authors suggest that now the pendulum has swung about as far as it can toward an emphasis on benefits (Id. at 28). The question is whether it is time for the pendulum to swing back in the other direction and eventually come to rest somewhere in the middle (Id.). Will IRBs be able to foster adequate protections ensuring a fair distribution of risks and potential benefits while, at the same time, fostering appropriate research ventures? Are IRBs sufficiently versed in the ethical requirements of human subject research in order to carry out their role, or are ethical considerations lost in the shuffle of everyday tasks? As discussed later, the goals of uniformity and efficiency in the regulatory scheme alone are not ethical goals. It must be remembered that the overriding consideration is respect for the human subjects, which dictates that they know that the decision to participate in research entails making a gift for the sake of others (Katz 1993, at 8).

CHAPTER 1

A. When and How Did Bioethics Develop?

Long before its crystallization as an academic discipline in the 1960s and 70s, bioethics was evolving from isolated inquiries, ideas and theories into a coherent and practical field. Today, people train as bioethicists and hospitals, universities, government organizations and private industry hire bioethicists, who use their training and skills to help make decisions regarding life or death issues in science and medicine. Bioethicists have achieved a seat at the decision-making table (Robertson 2008). Many commentators have chronicled the history and development of the field of bioethics, including much debate over how the name “bioethics” itself came to be. Was it Van Rensselaer Potter, Andre Hellegers, or Sargent Shriver who first devised the term?

Some believe Potter coined the term when he introduced it in his 1971 book entitled *Bioethics: Bridge to the Future* (Reich 1994). Apparently, Potter was the first to advocate establishment of a discipline of bioethics, which he explained as: “[B]ioethics is advanced as a new discipline that combines biological knowledge with a knowledge of the human value system... I chose *bio-* to represent biological knowledge, the science of living systems; and I chose *-ethics* to represent knowledge of human value systems (Reich 1994, at 321 quoting Potter 1975, 2297, 2299; cf. 1971, at 2). Potter's focus on building this new area of study was on survival: the questionable survival of the human species and the even more questionable survival of nations and cultures. His goal was

to promote an optimum environment to sustain and improve the civilized world by enriching individual lives and by prolonging the survival of the human species in a form acceptable to society (Reich 1994, at 322).

Meanwhile at about this same time, Hellegers was busy establishing what would come to be known as The Joseph and Rose Kennedy Institute for the Study of Human Reproduction and Bioethics, at Georgetown University. Reich reports that Hellegers believed that bioethics would be a unique discipline combining science and ethics. His Institute would be the world's first designed this way (Reich 1994, at 323). His vision was the professionalized combination of science/medical expertise and ethical expertise; with his Institute providing the initial step in promoting the research, educational and clinical aspects needed to implement this new discipline.

Added to the mix are the recollections of Eunice Kennedy Shriver describing how her husband, R. Sargent Shriver, devised the term “bioethics.” “I can remember in the living room one evening, Sarge came up with the phrase 'bioethics.' Andre Hellegers was there and so were some others. We immediately latched on to that.” (Reich 1994, at 325 describing Shriver 1978 memo). Given all of this history, Reich concludes a bilocated birth for “bioethics” in the 1970/71 time frame in both Madison, Wisconsin and Washington, D.C.

Perhaps, however, the early 1970s is too late to earmark as the “Birth of Bioethics.” Some may prefer to point to the November 1962 Life Magazine article by Shana

Alexander on the “God Committee,” actually titled *They Decide Who Lives, Who Dies*. This article details a “committee” or group of seven non-medical persons charged with deciding, on non-medical criteria, who would have access to a new life-saving technology, kidney dialysis, and who would die (Capron and Michel 1993). Many more people needed dialysis than could be accommodated by the limited resource available. Therefore, the solution was to ask this small group of nonphysicians to review the dossiers of the medically suitable candidates and select those most deserving of the life-saving technology. The idea of selecting suitable candidates for medical intervention was itself a new phenomenon in the early 1960s and garnered much attention when the supposedly anonymous committee gained public notoriety. In fact, Al Jonsen points out that public awareness of and sensitivity to discrimination was just coming of age in the early 1960s. Why should a new medical technology designed to save lives be a source of medical discrimination (Jonsen 1993)? Jonsen opines: “Bioethics was a creation of the times. It was conceived as a response to the new technologies in medicine, but it was gestated in a culture sensitive to certain ethical dimensions, particularly to the rights of individuals....” (Jonsen 1993, at 5).

Other observers might suggest that the seeds for many of the central bioethical issues originated even earlier than the 1960s and, in fact, focus on the standards for research on human subjects as articulated in the Nuremberg Code of 1947. At the time the Code was developed, many physicians thought the dictates too extreme and in need of softening. The 1954 Declaration of Helsinki accomplished this by allowing for greater researcher discretion. At the time, it was thought that “men of good character” did not

need the strictures of the Nuremberg Code to do the right thing. Furthermore, it was argued that the restrictions would not stop scientists not possessing good moral character, so the protections against acts such as those of the Nazi doctors were unnecessary in the United States (Moreno 2005).

Again focusing on the “when,” an earlier bioethics historian, David Rothman, points to the critical period of change as 1966-1976. These dates are bounded by the Henry Beecher expose on abuses in human experimentation, and the New Jersey Supreme Court decision in the Karen Ann Quinlan case. The National Commission for the Protection of Subjects of Biomedical and Behavioral Research (The National Commission) was established within this period (Rothman 1991). The impact of these events was to bring non-medical personnel into the medical decision-making process, giving medicine an exceptional prominence on the public agenda and making it the subject of popular discourse (Rothman 1991, at 3).

Beyond the “when” of bioethics is also the question of “how” this new discipline developed. Commentators have noted that one of the strengths of the field is that it is and has been interdisciplinary, drawing people not only from medicine, philosophy, theology, and law but also from nursing, medical anthropology, medical sociology and other related fields. Daniel Callahan noted: “Most practitioners have wandered into the field from somewhere else, more or less inventing as they go” (Capron and Michel 1993, at 26). This melding of many disciplines results in the absence of a single, accepted methodology in bioethics decision-making. The bringing together of philosophers,

theologians, physicians, lawyers, and other professionals leads to a cacophony of voices in addressing moral questions arising in medicine and biotechnologies. Fundamentally, bioethicists help answer questions that affect human life. They do so by providing input for the development and implementation of patient care guidelines and policies and by performing individual case consultations at the request of the physician, the patient or the patient's family (Robertson 2008, at 6). Surely, theologians and philosophers each confront the complex moral issues from their unique perspectives.

Theologians are concerned with how advances in science could lead to manipulation and alterations of human beings. Some believe the theological inaugural address for bioethics was given by a Protestant theologian, Helmut Thielicke, in 1968. Others cite a book written by Episcopal theologian, Joseph Fletcher, in 1954 entitled *Morals and Medicine*, in which the author departed from the usual theological analysis to stress the freedom and authority of the patient (Jonsen 1993, at 4). According to Jonsen, Fletcher's views led him to remarkably liberal positions about euthanasia and patients' rights. Another noted theologian, Paul Ramsey, authored an insightful analysis of the ways in which the new medicine was modifying the moral dimensions of the doctor-patient relationship in his 1970 book entitled: *The Patient as Person* (Jonsen 1993, at 4). It is not surprising that the problem of moral pluralism plagues any effort to settle on one satisfactory theological methodology for tackling bioethical problems. H. Tristram Engelhardt opines that we meet as "moral strangers," that is, people who do not "share enough of a concrete morality to allow the common discovery of the basis for the correct resolution of a moral controversy" (Engelhardt 1991). Engelhardt further opines

that even with this lack of moral community, it is still possible to at least establish procedural ethics based on respect for individuals as free moral agents (Engelhardt 1991, at 135).

Philosophers dealing with bioethics issues attempted to move beyond the theoretical toward becoming practitioners of medical ethics. The philosopher Stephen Toulmin advocated the position that American philosophy was changed by its encounter with medicine in *How Medicine Saved the Life of Ethics* (Jonsen 1993, at 6). Philosophers entered the world of medical decision-making in an effort to help shape the logic of moral judgments and to help doctors see patients as persons, and not just as collections of organs. Noted philosophers Beauchamp and Childress set about to establish guiding principles for bioethical decision-making. As opposed to Engelhardt, these philosophers started with a basic premise that there exists a “common morality,” or a set of norms, shared by all persons committed to morality. Not merely a morality, the common morality is applicable to all persons in all places, and we can rightly judge all human conduct by its standards (Beauchamp and Childress 2009). One of the primary authors of the *Belmont Report*, Tom Beauchamp, suggests that it is really the “common morality” that is the grounding for the principles ultimately featured in *Belmont*, and not the writings of philosophers. Beauchamp explains that the *Belmont Report*, in referring to “our cultural tradition” as the basis for the principles, makes it clear that they derive from the common morality and not from a particular philosophical work or tradition (Childress, Meslin & Shapiro 2005). As an aside here, it should be noted that the *Belmont Report* was a direct result of a legislative charge to the National Commission to

conduct a comprehensive investigation and study in order to identify basic ethical principles that would underlie the conduct of human subject research. The National Commission was further directed to recommend guidelines for such research that could then be supported by the Department of Health, Education and Welfare, the predecessor of the current Department of Health and Human Services (DHHS). The three principles ultimately embodied in the *Belmont Report* are respect for persons, beneficence and justice.

The first principle, respect for persons, affirms the view that if research involving human persons as subjects is to be considered an ethical activity it must, above all, be an activity freely entered into (Childress, Meslin & Shapiro 2005, at 7). However, as elaborated in the *Belmont Report* itself, respect for persons is said to incorporate “at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished capacity are entitled to protection” (Childress, Meslin & Shapiro 2005, Appendix). Likewise, the term “beneficence” in *Belmont* equates to not only the well-known adage guiding physicians: “do no harm.” It is also intended to express the intent to maximize possible benefits while minimizing possible harm (Id.). Justice was added to avoid burdening the indigent or the sick with research beneficial to others, the more well off. There was no attempt to balance or prioritize the three principles, which are proclaimed to be the pillars that uphold the ethics of research with human subjects (Childress, Meslin & Shapiro 2005, at 8).

B. And Now for the “Why”

Along with “when” and “how,” another segment of the development of bioethics must focus on the “why.” Although there can be no doubt that biomedical research has been responsible for a vast array of medical advances, it has also been a means through which horrific abuses have been perpetrated in the name of acquiring generalizable knowledge. It is just because of these abuses that medical research has become a tightly regulated enterprise over the past half-century (Pike 2012). From the beginning of the post-World War II era, the Nazi atrocities gave rise to the Nuremberg Code, the first generally accepted code governing research using human persons as subjects. During World War II, German physicians conducted horrific medical experiments on thousands of concentration camp prisoners without their consent. In 1946, an American military tribunal opened criminal proceedings against 23 leading German physicians and administrators for their willing participation in war crimes and crimes against humanity. The verdict was issued in August 1947, finding seven defendants guilty and sentenced to death, eight defendants guilty and sentenced to imprisonment and seven not guilty. The final verdict most notably contained a section entitled “Permissible Medical Experiments,” which later came to be known as the Nuremberg Code.

Two American doctors working on the prosecution team, Andrew Ivy and Leo Alexander, researched the history and practice of human experimentation and provided the data for the verdict's ten point analysis of acceptable medical experiments section. The first point, and recognized as the most important, is the necessity of obtaining authentic, uncoerced informed consent from the human subjects. It is stated as: “the

voluntary consent of the human subject is absolutely essential” (Schneider). This included sufficient knowledge and comprehension by subjects to make an understanding and enlightened decision. Reportedly, the most significant problem with the Code was with compliance and enforcement. In fact, the Nuremberg Code explicitly left this up to the experimenter. The final paragraph of the first point states: “The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity” (Schneider at 4).

All codes and regulations following the Nuremberg Code import some aspect of informed consent, with varying degrees of strictness and success. For instance, in 1953 the Clinical Center of the National Institutes of Health (NIH) produced the first federal policy regarding intramural research on human subjects, adopting the Nuremberg Code's emphasis on using healthy, competent volunteers in clinical research (Babbo 2000). The human subject was to be considered a member of the research team and afforded an opportunity to understand and comprehend the investigation contemplated with emphasis on the particular danger to him (Babbo 2000, at 3).

The next year, during its Eighth General Assembly, the World Medical Association (WMA) proposed its “Principles for Those in Research and Experimentation,” wherein the WMA introduced notions of substituted or surrogate consent by a subject's relative or legal representative. This ultimately led to the Declaration of Helsinki promulgated by the WMA at its 18th General Assembly in 1964 in Helsinki, Finland. This document

became the standard for medical research with patients as subjects, as it was the first significant effort by the medical community to regulate itself and, as such, was endorsed by and received acclaim from the medical community, particularly in light of its non-legal, advisory nature. By order of priority, the Declaration placed scientific expertise and the goals of medicine before the informed consent of the research subject and allowed research on those incapable of providing informed consent in certain circumstances, where proxy consent was available (Babbo 2000, at 3), (Pike 2012, at 4). Informed consent was a far less prominent feature of the Declaration than of the Nuremberg Code (Moreno 2005). The Declaration distinguished between therapeutic and nontherapeutic research, defining the former as “Medical Research Combined with Professional Care.” According to Helsinki IV (1989), “If a physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee” (Moreno 2005, at 123). Thus the Declaration, even as late as 1989, continues to enforce the rather permissive attitude toward investigator discretion.

Despite being revised many times, as recently as 2000, there remained reasons why some noted commentators believed the Declaration was in need of significant revision. According to Robert Levine, the distinction between therapeutic and nontherapeutic research is nonsensical and even though this specific language has been removed over the course of revisions, the document still relies on this distinction (Levine 2002). This surviving distinction is a logical flaw that persists in the Declaration, according to Levine. To have a category of “therapeutic research” is incoherent when at least some

component of research is always necessarily nontherapeutic. Only research that is entirely nontherapeutic can be called “nontherapeutic” so that when entire research protocols are evaluated as either therapeutic or nontherapeutic, it ends up as what Levine calls the “fallacy of the package deal” (Levine 2002, at 559-560).

Levine further opines that the Declaration is seriously out of touch with contemporary ethical thinking in its unnecessarily rigid stance against placebo controlled clinical trials (Levine 2002, at 558). Beginning in 1975, the Declaration, as then revised, provided that every patient, including those in a control group, should have the best proven therapeutic methodology available. It did allow for the use of some placebos, but only where no proven therapeutic method existed (Jost 2000). The WMA substantially revised the Declaration at its Fifty-second Assembly in 2000 in response to intense public responses to some of its outdated provisions, adding new ideas that had not appeared in previous versions (Grady 2005). However, Paragraph 29 as clarified by WMA in 2002, still maintained a definitive stance against placebo-based trials if an alternative treatment exists (Grady 2005, at 428). Another hot button in the Declaration is Paragraph 30, which deals with post-trial access by study participants to therapeutic interventions identified as beneficial. As revised, Paragraph 30 requires that post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review (Grady 2005, at 428).

As for the NIH, in 1966 it expanded the 1953 guidelines beyond intramural research to include extramural as well. The then-director of NIH, James Shannon, believed that

some research conducted outside of government oversight was not sufficiently controlled and potentially damaging to NIH's reputation. Shannon wanted NIH to take a leadership role in protecting research participants. He proposed a system whereby grantee institutions would have to create a committee to provide impartial peer review of risks and benefits posed by research before the research could begin (Riley 2011, at 272). Under the 1966 Public Health Service Policy Regarding the Protection of Human Subjects, the NIH would only approve extramural research grants for those institutions having an internal review board charged with protecting the research subject. The Policy included a provision that the informed consent process and forms were to be open to review and approval by the internal review board. Thus, in 1966, the NIH Policy was a harbinger of the current practice of Institutional Review Boards (IRBs) under the federal regulations (Babbo 2000, at 4).

Reportedly, there was a fair amount of resistance to the 1966 NIH policy guidelines, with review committees complaining of overwork and some researchers refusing to cooperate. In 1971, a new guide was issued: *The Institutional Guide to DHEW Policy on Protection of Human Subjects* (the Yellow Book). The Yellow Book provided a structure similar to that which guides biomedical research under the federal regulations today. Like its predecessors, the Yellow Book required the use of institutional committees and provided guidance on the composition and duties of those committees (Riley 2011, at 272). It also required that each committee establish guiding principles for its work but, unfortunately, with no insight into the substance the principles should contain (Riley 2011, at 273).

NIH took note of research ethics after the 1962 Kefauver hearings exposed physicians administering experimental drugs without informing patients. NIH immediately commissioned an investigation, resulting in the 1964 Livingston Report. The authors of the report recognized mounting concern over possible repercussions and untoward events, as there were no generally accepted professional standards relating to the conduct of clinical research (Rothman 1991, at 87). Notably, the Report's authors concluded that whatever the NIH might do by way of designing a code or stipulating standards for acceptable clinical research would be likely to inhibit, delay, or distort the carrying out of such research, rendering any such constraints unacceptable (Rothman 1991, at 87). The implicit assumptions in the early to mid-1960s were that no imposition of standards could justify hindering the progress of clinical research. This thinking was about to change.

In 1966, the *New England Journal of Medicine* published an article authored by Henry Beecher, a Harvard medical school professor, reporting twenty-two examples of abuses to research subjects occurring between 1945 and 1965. Beecher used published research protocols taken from leading, mainstream medical journals to find examples of abuse. The examples included researchers at such well-respected institutions as Duke, Emory, Harvard, and NIH. Instances of abuse included purposely giving mentally impaired children a mild form of hepatitis to study the infection, and injecting cancer cells into patients without telling them that the cells were cancerous. Worst of all, all but two of the examples lacked any form of voluntary, informed consent. Most of the research subjects were marginalized populations, including mentally retarded,

institutionalized, senile, and alcoholics, as well as the poor and soldiers. Children and the aged were included in the studies and, ironically, it was the subjects' alleged incompetence that researchers relied on as the reason that informed consent was not needed. Claiming that the subjects would not have understood anyway, the researchers were able to confidently assert their right to exercise discretion and to substitute their own judgment (Rothman 1991, at 80). It is interesting to note that, despite the revelations in his article, Beecher was reluctant to condemn the researchers' actions or to push for new, stricter rules or regulations. In fact, he maintained that it was thoughtlessness and carelessness, not a willful disregard of the patients' rights, which accounted for most of the cases encountered. Believing that calling attention to the abuses would help to correct the problem, he appealed to the professional trust and responsibility of the medical researchers (Rothman 1991, at 83, 84).

By today's standards, these researchers would have been sanctioned and their institutions severely penalized for such research abuses. The lack of informed consent and the significant risk to the subjects with the minimal, if any, benefits are violations of our present day understanding of the regulations. Commentators have noted that in the post-World War II era, there was a strong belief in researchers' achievements and the power of progress. Beecher himself is said to have recognized the power of progress and to have commented, "In some sophisticated circles there is a belief that attention to ethical concerns would block progress" (Beecher 1966, at 1354). He argued that the presence of an intelligent, informed, conscientious, compassionate and responsible investigator offered the best protection for human research subjects, without the need for ethical

review committees (Harkness, Lederer & Wikler 2001). Belief in the progress of scientific research infected the public as well as scientists in this era, which Rothman calls “the gilded age of research, the triumph of laissez-faire in the laboratory.” Public policy focus was not to check the discretion of the investigator but to free up funds to expand the scope and opportunity for research (Rothman 1991, at 51).

As noted above, in 1966, NIH promulgated guidelines for federally funded research. These regulations may well be considered a Beecher legacy. Essential components of the '66 guidelines were predecessors to the current regulation requirements of informed consent and IRB review. The most important features of the review process were that it included reviewers from outside the project and the medical community, and that it tied funding to compliance, thereby establishing an enforcement mechanism. At this time, the overall approach was to assign local institutions the bulk of the oversight responsibilities. Local institutions receiving federal grant money were to maintain documentary evidence of both informed consent and review of research protocols by a review committee not directly associated with the project. It was the opinion of NIH at the time that review by a board offered better protection than informed consent, since it was deemed not possible to convey all the information to the subject upon which he could make an intelligent decision (Rothman 1991, at 89).

Any historical time line leading up to the establishment of federal regulations governing research with human subjects must include a discussion of the infamous Tuskegee syphilis experiment. Known at the time as the Tuskegee Study of Untreated Syphilis in

the Negro Male, it was the longest nontherapeutic experiment on human beings in medical history (Jones 1993). It began in 1932 and was conducted by the U.S. Public Health Service (PHS); six hundred low-income African-American males from rural Alabama with a high incidence of syphilis infection were monitored for forty years. In the early 1930s, syphilis, a sexually transmitted disease full of moral stigma and dangerous health effects, was a widespread problem in many communities across the country. As part of its effort to reach out to underserved rural black communities in particular, the Rosenwald Foundation (a major Chicago-based philanthropic devoted to black education in the south) and the PHS set up a demonstration project in six southern states to track and treat the disease. When funds dried up in the Depression, the PHS's idea was to study, in one county, what happened without treatment (Reverby 2010).

The county was Macon County, Alabama, where the PHS and the Tuskegee Institute together enrolled 399 Black sharecroppers who had previously contracted syphilis and 201 men without the disease. For participating in the study, the men were given free medical care, meals and burial insurance. They were never told they had syphilis nor were they ever completely treated for it. The men were told they had “bad blood,” a local term used to describe several illnesses, including syphilis, anemia and fatigue (Jones 1993, at 5, 6). The men were initially studied for six to eight months and then given at least partial treatment with then contemporary methods, including bismuth, mercurial ointments and such. These methods were mildly effective at best. In addition, a magic bullet was discovered by a German scientist, Paul Ehrlich. Salvarsan, a preparation of organic arsenic, was reported to cure syphilis. The highly toxic drug, together with

spinal punctures, was administered to the study participants, resulting in great pain and discomfort (Jones 1993 at 45, 46, 112). Monies for the treatment phase of the study were withdrawn when the Rosenwald Foundation suffered the effects of the 1929 Stock Market Crash. Medical ethics considerations were sketchy at best and deteriorated rapidly once funding was withdrawn. To ensure that the men would show up for the possibly dangerous, painful diagnostic and nontherapeutic spinal taps, the doctors sent misleading letters to 400 of the participants claiming it was the last chance for “special free treatment” (Jones 1993, at 109).

By 1947, penicillin had become the standard therapy for syphilis. The U.S. Government sponsored several public health programs to form treatment centers to eradicate the disease. When campaigns to eradicate venereal disease came to Macon County, study researchers prevented their patients from participating. The Tuskegee scientists continued the study without treating any of the participants, and withholding penicillin and information about it from them. The study continued under numerous PHS personnel until 1972, when a leak to the press eventually resulted in its termination. Reportedly, the facts and data regarding the Tuskegee Study were literally dropped in the lap of Jean Heller, a highly regarded, young reporter who worked in the research bureau of the Associated Press in Washington D.C. Heller broke the story on July 25, 1972 in the Washington Star. The following day, a high-ranking official at the Department of Health, Education and Welfare (HEW), the successor agency to the PHS, expressed shock and horror and established an ad hoc panel, vowing a full investigation into the facts and circumstances surrounding the study (Jones 1993, at 204, 206). The ad hoc

panel's first report, issued in late April 1973, was highly critical of the entire study, judging it “ethically unjustified in 1932” (Jones 1993, at 211). That decision rested on the government's failure to obtain informed consent from the participants in a study of a disease with known risk to human life. The panel also found that penicillin therapy should have been given once it was generally available, and certainly no later than 1953. Finally, the panel urged that existing protections for human subjects of experiments were not effective and called for greater procedural and substantive safeguards. The most important recommendation was to call upon Congress to create a permanent body to regulate all federally sponsored research on human subjects (Jones 1993, at 211, 212). At the time this report was issued, Senator Edward Kennedy was already conducting a series of hearings before a subcommittee on health, part of the labor and welfare committee, to deal with human experimentation issues. The Kennedy hearings presaged a national review of federal guidelines on human experimentation and a call for reform. More than any other experiment in American history, the Tuskegee Study convinced legislators and bureaucrats alike that tough new regulations had to be adopted if human subjects were to be protected (Jones 1993, at 214).

It should also be noted here that during the course of the 40 year Tuskegee Syphilis Study, other similar research was being conducted in Guatemala. It was not revealed until 2010 that United States researchers used prostitutes to infect prisoners, insane asylum patients and Guatemalan soldiers with syphilis and other sexually transmitted diseases from 1946 to 1948. Approximately 700 people were infected as part of the study, including orphan children. As with the Tuskegee study, this study was also

sponsored by PHS, this time in conjunction with NIH, the Pan American Health Sanitary Bureau and the Guatemalan government. Also of note, the study team was led by John Charles Cutler, who later participated in the Tuskegee study. Cutler chose to do the study in Guatemala under the guise of providing syphilis inoculations because he knew it would not have been permitted in the United States. Reportedly when some of the subjects failed to contract the disease, researchers created abrasions on their bodies and poured the bacteria right in. In 2010, these experiments were revealed by Susan Reverby of Wellesley College, who learned about them while researching a book on Tuskegee. This led to formal apologies by both then Secretary of State Hillary Rodham Clinton and President Barack Obama, calling these experiments “a crime against humanity” (Stein 2010).

C. And Where Did This All Lead?

Largely in response to the Tuskegee scandal, Congress passed the National Research Act of 1974. The Act established the Office for the Protection from Research Risks (OPRR) as part of NIH and set up the 11 member National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (the National Commission). The mandate given the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines that should be followed in the conduct of such research (Jonsen 1998, at 98, 99). As noted by Jonsen, “No legislation had ever before charged a government body ‘to identify basic ethical principles’” (Jonsen 1998, at 98).

While some may have questioned the Constitutional or other power or authority of Congress to mandate a group to determine what is ethical, that is exactly what was done. The 11 member Commission, appointed by then Secretary of HEW, Joseph Califano, consisted of three physicians, two biomedical researchers, three lawyers, one public member and two philosophers. The mandate required the Commission to study the ethical questions raised in the use of several particular populations in research: the fetus, children, the institutionalized mentally infirm, and prisoners. Noted theologians of the time were engaged by the Commission to aid in their research and deliberations. To further aid the Commission in identifying the ethical principles to be used in federally funded research, a meeting was held in 1976 at Belmont House, a conference center of the Smithsonian Institutes at Elkridge, Maryland. The central question of this meeting, known as the Belmont Conference, was to reconcile protection of subjects with research goals. Several essays were presented at the meeting and, as reported by Jonsen, the final establishment of three basic principles to govern human subject research was a collaborative effort. Tris Engelhardt suggested the first two principles: respect for persons and research that benefits society. Tom Beauchamp proposed the final principle that was adopted, distributive justice. Thus, it came to be that the Conference adopted the three “crisp” principles: respect for persons, beneficence and justice (Jonsen 1998, at 102, 103). The actual document went through several drafts and iterations before being issued in final form as *The Belmont Report* in 1978. With this report, the Commission satisfied part of its Congressional mandate by identifying three ethical principles for the government to use in evaluating issues concerning research using

human subjects: respect for persons and protection of the decisionally impaired, beneficence and justice. These came to be known as the Belmont principles.

Jonsen describes the influence of the Commission on the ethics of research with human subjects in four main areas: clarifying the definition of research, promoting the consent process to prominence, unraveling the paradoxes of research with persons of diminished capacity to consent, and moving the research debate into the public sphere (Jonsen 1998, at 151). Not surprisingly, the *Belmont Report* has been called the crown jewel of the Commission, providing legislatively mandated philosophical underpinnings of the structure for regulation as required by the National Research Act. The authors of the *Belmont Report* did not see their role as providing a rationale for the ethical directives of respecting persons, doing good, and upholding justice. The Commission purposefully avoided definitions that might answer difficult questions on personhood or the like. In fact, the Report was viewed more akin to a regulatory Nuremberg Code. In light of the findings in the *Belmont Report*, as well as those found in similar reports by the Commission concerning research on pregnant women, children, the mentally disabled, and prisoners, HEW's successor, the Department of Health and Human Services (HHS) used it to revise its existing regulations in 1979 (Babbo 2000, at 395, 396). Two years later, in 1981, HHS promulgated new regulations concerning research on human subjects. For the next twelve years, these regulations governed only research sponsored by HHS. However, in 1991, sixteen federal agencies incorporated the HHS regulations into their own codes regarding the protection of human subjects, becoming what is known as the Common Rule. As Beauchamp says of the Belmont Report, "it is one of the few

documents that has influenced almost every sphere of activity in bioethics and its principles became the backbone of federal law governing research involving human subjects” (Pike 2012, at n 61 quoting Beauchamp 2006).

The cornerstone of human subject research regulation is the IRB. Today, the principles and analysis set forth in the Belmont Report serve as fundamental references for IRBs that review research protocols, whether conducted or approved by federal agencies or in universities or other research settings. Therefore, it is against this backdrop that we begin to examine a critical component of human subject research oversight, the IRB.

CHAPTER 2

A. The Structure and Functioning of Institutional Review Boards

In its 1978 report on IRBs, the National Commission explained that the ethical conduct of research requires a balancing of society's interest in protecting the rights of subjects and in developing knowledge that can benefit the subjects or society as a whole (Goldner 1993). The IRB Report found that investigators should not have sole responsibility for determining whether research involving human subjects fulfills ethical standards. Others who are independent of the research must share this responsibility, because investigators are always in positions of potential conflicts by virtue of their concern for the welfare of human subjects while pursuing knowledge (Goldner 1993 at 100). Further, the rights of subjects must be protected by local review committees operating pursuant to federal regulations and located in institutions where research is conducted (Id.).

An IRB is not a branch of a regulatory agency or a governmental function, although the regulations call for registration of IRBs with the Office for Human Research Protection (OHRP). Rather IRBs derive their authority from the academic institution of which they are a part or, if independent, from the organization or business entity that hired them. An IRB is a board, committee or other group designated to review, to approve the initiation of, and to conduct periodic reviews of clinical research studies involving human

subjects. Once established, the IRB must act in conformance with the federal regulations. (Williams, et al 2007, 21) The regulations, which set out criteria for approval, require the IRB to assess a variety of scientific and ethical factors. Some may argue that IRBs have quasi-regulatory functions, but they are not technically governmental agencies and do not exercise full regulatory powers. While it is true that governmental agencies do rely on IRBs to monitor and safeguard research participants in compliance with the federal regulations, they are, at most, an example of an “audited self-regulation system” (Saver 2004, at n. 34 quoting Noah and Noah 2002).

The primary purpose of the IRB is to ensure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in research. IRBs act as a group to review research protocols and related documents, to ensure that the risks and benefits of any proposed research are balanced, that there is an equitable selection of participants and that the consent forms are valid. Board members must seek to ensure fair subject selection, consider whether participation can be freely chosen by those to be recruited, and whether adequate privacy protections are in place. Importantly as well, they evaluate whether the risk of harm is minimized and whether the risk of harm is reasonable in relation to the anticipated benefits, if any, to the subject and to the importance of the knowledge expected to be gained. They also are charged with determining the adequacy of the plans to obtain subjects’ informed consent (Eckenwiler 2001, at 39). IRBs must assess the broader scientific merit of each research proposal, a task that includes risk-benefit analysis, while considering the research plan in the broader arena of scientific inquiry (Noah 2004, at 187). Thus, as

Eckenwiler opines: “Their mandate ... is to amass information about each protocol, to determine whose interests are at stake, to evaluate whether established criteria have been met, and to consider how these should be interpreted, described, and ultimately addressed in order for a given project to gain approval and to be carried out” (Eckenwiler 2001, at 39).

Federal regulations require that, to be valid, an IRB must have at least five members, including one member from the community at large and not affiliated with the institution, and one non-scientist. IRBs should strive for diversity in membership. Research is reviewed at convened meetings with a majority of the members or a quorum present, but regardless of the number of members in attendance, the meeting cannot proceed in the absence of the community member. Research is approved by majority vote of those present. An IRB may approve a research protocol, approve it with modifications, disapprove it or table it for later reconsideration after revisions or additional information is provided. The federal regulations further specify the type of person who should serve in the IRB process in order for a complete and adequate review to be accomplished. First, the boards should include those individuals with the professional competencies necessary to review specific research activities, including scientists and health care professionals (Eckenwiler 2001, at 39). The regulations also encourage IRBs to include members who are knowledgeable about and experienced in working with those who are described as “vulnerable” populations. Consideration should be given to diversity in race, gender, and culture in membership to “display sensitivity to such issues as community attitudes” (Eckenwiler 2001, at 40).

IRBs' responsibilities do not end when the initial review is complete. They must conduct continuing reviews, generally annually, of ongoing research protocols. IRBs have authority to suspend or terminate research projects that fail to adhere to the requirements of the original approval. IRBs can stop research that leads to unexpected, serious harm to subjects. IRBs require researchers to report adverse events concerning any unexpected complications or effects on subjects. Research can then be suspended, terminated or modified as warranted (Saver 2004, at 643). Indeed, it is in the role of continuing review that IRBs are sometimes faulted for not seeking out more information. The process seems perfunctory and not likely to catch developing problems, presumably because so many IRB members treat continuing review as a very minimal review. Reportedly, one IRB member told the Office of Inspector General that he reviews the continuing review summaries during the board meetings to see if a patient has died. If no patient has died, then he generally does not raise any questions (Hoffman 2001, at 733).

B. Do IRBs Impede Social Science Research?

This relaxed attitude is in sharp contrast to the voluminous literature focused on researchers complaining about and commenting on the difficulties of getting research approved, with the concomitant concern about the IRBs' potential for exerting a chilling effect on research with human subjects. Some commentators opine that important scholarship can be lost or compromised when research proposals are subject to over-

bureaucratization and inefficiency, with the most common complaint being time delays. Another frequent complaint relating to IRBs is mission creep. The argument centers on the presumed overwhelming expansion of the original purpose of IRBs, to review biomedical research, into softer social sciences, legal academic studies, journalism and large segments of the humanities (Katz 2007). This is what Katz calls ethical censorship. Another author, Zachery M. Schrag, in his 2010 work entitled: *Ethical Imperialism*, particularly focuses on the chilling effect the regulations, in particular, IRB review, have on social sciences and humanities (Schrag 2010). Schrag says it was really Al Jonsen who coined the phrase *ethical imperialism* to describe the imposition of one field's rules onto another discipline (Schrag 2010, at 9). Schrag's basic premise is that regulators forced social science research into an ill-fitting biomedical model to the detriment of the social sciences (Id.). Despite this, Schrag opines that social scientists and IRBs were able to live in a rather peaceful accord through the 1980s and into the early 90s. While IRBs reviewed social science research, it was characterized as a "gentle" review (Schrag 2010, at 126). This all changed as policymakers responded to scandals or perceived scandals in medical research with an increasingly stricter regulatory review and with no exception allowed for social science research.

Sparking this change was a 1993 series of articles run in the *Albuquerque Tribune* by reporter Eileen Welsome regarding radiation experiments. It seems that eighteen Americans were injected with plutonium in the 1940s as part of a government-sponsored research project on the effects of radiation. This was then widely reported and became a second Tuskegee (Schrag 2010, at 130). In response, then President Clinton created

the Advisory Committee on Human Radiation Experiments (ACHRE) to investigate and make recommendations on how the federal government should deal with past abuses and how to prevent future ones. President Clinton further, and importantly, directed all federal agencies to review human subject regulations and to immediately cease any research that does not comply with the regulations. Thereafter ACHRE issued a report citing problems with the IRB system (Schrag 2010, at 130,131). The committee found that IRBs spent too much time on research protocols with minimal risk and did not have sufficient time to devote to those truly risky. The effectiveness of federal oversight then became the focus of the National Bioethics Advisory Commission (NBAC) established by President Clinton. By May 1999, the NBAC reported to the President that Americans involved as subjects in research were vulnerable, as regulations were not evenly applied and enforced. While finding no instances of the gross abuses of the past, the NBAC still wanted to err on the side of caution, calling for more oversight. This led to more work for already overworked IRBs. NBAC recommendations translated into longer consent forms, more training, more paperwork and more inspections of IRBs (Schrag 2010, at 131). Exemptions to IRB review were more strictly applied in this era and none existed for social science research, thus, social scientists were caught up in the expansion of the federal oversight.

Some commentators evaluating IRB review of social science or any non-medical research find it to be adversarial rather than a complementary or collaborative process (Nicholls, Brehaut, Saginur 2012). This adversary type relationship may be attributable to the regulatory mandate imposed on IRBs. They are specifically established to protect the

rights and welfare of the subjects and not the researchers. It is also clear that the regulations were designed to deal with biomedical research but have been applied across all disciplines that involve humans. Short of drafting separate regulations applicable to non-medical research, the current regulations will and should continue to apply. Non-medical researchers have some options under the current regulatory scheme. They could apply for exempt or expedited status if the proposed research protocol qualifies. Separate non-medical IRBs can be created or, for that matter may already exist at some large research institutions. Existing IRBs can seek to include more behavioral or social scientists. However, some may argue these options are insufficient to curb the mission creep of regulation from biomedical to behavioral research, and further contend that non-medical research should not be subject to ethical review under the current regulations at all. This is akin to throwing out the baby with the bathwater. Better guidelines for review of social science research and better education of IRBs may be warranted but do not support the notion of no ethical review. Social sciences can pose long-term and serious risks to subjects from such things as psychological trauma, invasion of privacy and the like. These may seem innocuous when compared to the atrocities of Nazi medical experiments, but still signal the potential for abuse and serious adverse effects (Nicholls, Brehaut, Saginur 2012, at 72).

One particular study that highlights risks imposed by social science research is what has become known as the Milgram Experiment, so named for the researcher who devised the study, Stanley Milgram. Milgram researched the effect of authority on obedience in a study conducted at Yale University in 1961. He advertised for participants to take part

in a study of learning and memory. One participant would be the learner and one the teacher. The teacher would be responsible for shocking the learner every time the learner got an answer wrong. Each successive wrong answer resulted in an increased shock voltage. The teacher did not know that the learner was a trained person working with the experimenter or that the shock machine was a fake (Herrera 2001). Many of the subjects continued shocking learners for wrong answers when they were instructed to do so, despite reservations about continuing. Milgram reported that the experiment created extreme nervous tension in some subjects including one subject who was reduced to a twitching, stuttering wreck, approaching a point of nervous collapse (Milgram 1963).

This is certainly an example of research without adequate informed consent. How could a subject give truly informed consent when being deceived? Informed consent should mean, at a minimum, that subjects are given adequate descriptions of the risks they may face. Here the subjects believed they were participating in a study on learning and memory, not obedience to authority. Furthermore, no one was informed that they would be asked to administer pain to “learners” who make mistakes. While Milgram and others tend to justify the deception as necessary to insure that the subjects will act naturally, it still raises ethical issues that require oversight and independent review despite retrospective dehoaxing or debriefing.

Social scientists have made some headway in limiting IRB oversight. In 2003, OHRP, in conjunction with the Oral History Association and American Historical Association, issued a formal statement that taking oral histories, unstructured interviews, collecting

anecdotes, and similar free speech activities often do not constitute “human subject research” as defined in the regulations and were never intended to be covered by clinical research rules. IRBs have some flexibility and should rely on common sense in evaluating research protocols. This principle dates back to the *Belmont Report*. Ethically sound research requires flexibility and a balancing of factors in decision-making (Levine and Skedsvold 2008).

C. Further Abuses Despite IRB Review

IRB review of research protocols, no matter how exacting, does not guarantee that no mishaps occur and research involving human subjects sometimes extracts a high price from those who participate. Recent events have drawn public attention to flaws in the regulatory system that is designed to protect such subjects and have prompted demands for reform (Noah 2004, 176). Although calculating the number of research-related deaths and injuries has proven to be difficult, it is estimated that as many as 5,000 may die annually in federally funded research protocols (Id.). The following sections of this part of Chapter 2 will provide details relating to three well-documented research mishaps.

1. Estate of Gelsinger v. Trustees of University of Pennsylvania

An unfortunate situation in human subject research with far-reaching consequences is found in the case of Jesse Gelsinger. Jesse died while participating in a human gene therapy trial at the University of Pennsylvania (Penn). Jesse has born with a mild form of

a rare metabolic disorder affecting his liver. Because of the defect, nitrogen normally discharged in urine turned into ammonia in his body. This is known as an OTC deficiency or OTCD. The traditional treatment has been a regimen of special diets and daily medications. Researchers at Penn were developing a gene transfer to release patients like Jesse from OTCD's hold, particularly focusing on newborns with this genetic condition. The researchers were ready to proceed with Phase 1 human subject trials in 1998/9. In June 1999, Jesse and his father, Paul, visited Penn to see if Jesse was eligible to participate in the trial. During that visit, Dr. Steve Raper went through the Consent Form with Jesse and Paul. Jesse understood that if the trial was a success, there would be no lasting benefit to him, but that the intervention might later provide relief from the disease in newborns. The Consent Form did raise the possibility of death and caused Paul to caution his son about the seriousness of the trial.

Jesse participated in the Phase 1 clinical trial, designed to test the safety of the intervention, not its efficacy, which usually is tested in later phases. Jesse was part of a stair-step dosage trial designed to include 20 total subjects. Jesse was participant OTC. 019 and received the highest dosage (Wilson 2010). Jesse was infused with the vectors on September 13, 1999, despite the fact that his ammonia levels at that time were in excess of allowable levels in the protocol approved by the Penn IRB. Jesse died on September 17 as a result of a total organ failure caused by a massive immune system response (Wilson 2010, 295). A major question after Jesse's death was whether Jesse and his father were told the truth about all of the risks that Jesse would face in the trial, and whether information left out of the IRB approved consent form would be material to a reasonable person in the position of Jesse and his father.

The answer to these questions is clear from the scant record available. The whole truth about risks was not disclosed and the information not included would certainly be material to a reasonable person under the circumstances. Unfortunately, since the case settled within about 6 weeks of being filed, there is no official record and certainly no discovery of what actually happened. However, many articles and news stories have been written about this groundbreaking case. In fact, two lawsuits were filed and both settled before trial. It is documented, however, that critical information was left out of the consent form after it had been approved by a Penn IRB. This included the deaths of monkeys in a previous study of the intervention and other adverse events that should have been, but were not, reported to the FDA. Prior to knowing this, Paul Gelsinger defended the researchers at Penn and claimed his son was a hero for submitting to the trial for the benefit of others. After disclosures about the prior trials, as well as the significant financial interests of the researchers, Paul Gelsinger did an about face and sued the researchers, the hospital, a bioethicist and many others under several novel legal theories (Id.). In addition to the Gelsinger tort suit, the federal government sued for alleged errors in the research trial under the civil False Claims Act. As stated, both of these suits settled, with no public apologies or admissions of wrongdoing. The defendants (or their insurers) in the government's suit paid about \$1M in damages to settle the government's claims. The amount of the Gelsinger settlement is sealed.

One thing is clear from the facts of this case: the researchers and the institution had substantial financial interests in the outcome of the trials. What we do not know is the exact nature of the financial stakes that the researcher, Dr. Wilson, and Penn had in the research's outcome, or why Penn allowed a researcher with substantial stakes to be involved in the research in the first place. We do know that there were clear and material departures from the approved protocol, unapproved changes to the consent form and records showing four successive volunteers suffered side effects so serious that Penn should have halted the study and notified the FDA. We know that Wilson owned shares in Genovo, the biotechnology company developing the vector for delivering the gene therapy. We know that Penn stood to share in financial gains through Genovo's success in the therapy. We also know that these financial stakes were not disclosed to Jesse or to his father in the Consent Form.

The federal conflict of interest and disclosure rules have not changed substantially in the decade since Jesse's death. The rules require researchers to disclose significant financial relationships, defined as \$5,000. in equity, salary or other thing of value. Penn had the responsibility to control or manage any conflict of interest in the conduct of the research trial. Penn should have, at least, kept Wilson at arms- length from the day-to-day decisions involved in the trial. Instead, documents and Wilson himself indicate that he was “hip deep in decisions affecting Jesse's trial” (Wilson 2010, at 301). As part of the government settlement, Wilson was required to write a “Lessons Learned” article before he could actively return to the clinical research. The article was finally published in 2009.

(Wilson 2009) In the article, Wilson acknowledged that he founded a biotechnology company focused on gene therapy while being directly involved in gene-transfer clinical trials as a sponsor of the new protocol. Thus, Genovo's success would have inured to the financial benefit of Wilson. However, this still does not mean that Wilson would have made different decisions in conducting the clinical trial but for his financial stakes. In fact, Wilson seemed to find it offensive that people believed his motivation for the trial was financial. He clearly iterated that it was not financial but ego. Wilson wanted the less overt rewards; prestige, fame, and professional pride. Wilson admits he was driven by leadership, lust for academic recognition and advancement and publishing in first-rate journals. Wilson's ambition and complex motivations provide fodder for those who believe there is really no way to avoid conflicts of interest in research, even with appropriate IRB review. There need not be direct financial benefit to motivate someone to proceed on the ethical fringes with clouded judgment in order to achieve a sought after outcome.

In 2008, Paul Gelsinger authored a paper with Adil E. Shamoo contending that, in the eight years since Jesse's death, nothing had really changed in human subject research. Despite the press exposure and public outcry that followed Jesse's death, people are no safer and are still at serious risk of exploitation and harm (Gelsinger and Shamoo 2008). Gelsinger maintains that many factors account for the absence of better protections, but perhaps the greatest obstacle is the lack of adequate federal oversight. One clear factor is the increase in privately or industry funded research to which the federal regulations may

not apply since the regulations technically only apply to research that is federally funded. However, as a condition to receiving federal funding, an academic institution formerly needed to agree or give assurances that, it would apply the federal regulations to all academic research. This trend has diminished recently. In 2010, it was reported that informational research was compiled on the federal-wide assurance status of 146 institutions for which OHRP had issued a compliance determination letter between 2002 and 2007 as compared with 155 institutions receiving such letters between 1998 and 2002. The results showed that over 90% had agreed to extend the regulations to all research, regardless of funding source, in the 1998-2002 sample as opposed to 74% in the 2002-2007 sample (Weil, Rooney, McNeilly, Cooper, Borrer, Andreason 2010).

Another obstacle to adequate federal oversight is the limited HHS and FDA resources, making any interventions into clinical trials a retrospective activity rather than proactive oversight of human subjects (Id.). In trying to discover the facts surrounding his 18 year old son's death, Gelsinger joined up with Adil Shamoo and members of his organization, Citizens for Responsible Care and Research (CIRCARE), a nonprofit dedicated to improving the protection of humans in research. Gelsinger and CIRCARE worked to promote federal legislation to safeguard research participants including requiring education and training for all investigators involved in clinical trials, reporting of all adverse events to a central national office, and strictly managing any conflicts of interest. It would also require that the majority of an IRB's members come from research institutions other than the ones involved in the study. It is easy to see that certain

provisions of the proposal could be disfavored by institutions. Since research is very competitive, grant monies highly coveted and prestige always on the line, it is unlikely an IRB constituted as proposed would win favor.

In his Lessons Learned paper, Dr. Wilson provides some guidance for the future of clinical trials. Lesson #1: *A clinical protocol is a contract with the research subjects and the regulatory agencies and must be strictly and literally adhered to.* That did not happen in Jesse's clinical trial. Lesson #2: *If you think about reporting-then do so.* If something seems like a reportable event, it probably is. Dr. Wilson concludes that any pre-clinical or clinical data that could have an impact on the study should be reported promptly to the IRB and to the FDA. This too did not happen in Jesse's trial. Lesson #3: *It is very hard to manage real or perceived financial conflicts of interest in clinical trials.* Wilson concludes that there is no difference in the management strategies for real or for perceived conflicts of interest in clinical trials. It appears that Wilson re-thought his original contention that he absolutely did not have a financial conflict of interest. Rather, in acknowledging the quest for academic pride and authorship, some financial rewards follow and, in essence, cannot be separated or compartmentalized. However, Wilson does not advocate zero tolerance here as it could have a chilling effect on research. Lesson #4: *Informed consent may require objective third party participation.* Wilson recognizes two challenges to a valid, fully informed consent in the gene-therapy study. First, it is hard with a new protocol to have the form in language that is understandable to the prospective participant. There are no explicit guidelines from the FDA or the Office of

Human Research Protection (OHRP). The second challenge relates to the natural tendency for individuals heavily invested in time and effort (not financially) in a cutting edge protocol to truly believe in the new technology. This “belief” makes it difficult to objectively represent its potential limitations to research subjects in the context of informed consent. While efforts were made to manage these challenges, Wilson admits they could have done better. (Wilson 2009, at 155,157)

2. Grimes v. Kennedy Krieger Institute, Inc.

In 1993, the Kennedy Krieger Institute (KKI), a well-respected, children’s health and research institute affiliated with Johns Hopkins University, began a two-year research study that tested lead paint levels both in residential homes and in children who lived in those homes (Adams 2002). At the time, approximately 95% of low-income housing in certain identified Baltimore neighborhoods had levels of lead contamination in excess of federally approved standards. Because minority and poor children tend to reside in older, poorly maintained homes built prior to 1978, when lead paint was banned, they are especially vulnerable (Beh 2002). Previous studies showed that 40-50% of the children living in these high-risk neighborhoods had elevated blood lead levels (Buchanan and Miller 2006). Eradicating the lead paint from all rental units would be extremely expensive. Sometimes landlords even abandon properties, leaving them vacant, rather than remediate the lead contamination in their units. KKI designed the research study to test low-cost lead abatement procedures in housing in Baltimore to determine their effectiveness in reducing blood lead levels in children living in those houses. The lead-

based paint had been in place for many years and was known to flake off. Children were apt to ingest these paint particles. Lead was further released into the atmosphere if paint was sanded off surfaces, for instance, windowsills, in preparation for repainting, with dust settling on children's toys, books, hands, etc. In the late 1980s, KKI had tested alternative, less expensive lead reduction methods in empty properties and demonstrated their effectiveness by showing that lead levels were reduced in lead paint dust by approximately 80% (Buchanan and Miller 2006, at 782). The next step was to propose a follow-up study to determine if the reduction in lead paint dust would result in lower blood lead levels in the children living in those houses (Id.).

KKI solicited participation in its study either by approaching the landlords of the low-income housing in Baltimore City or by approaching the tenants directly. To be eligible, KKI required that the children reside in the homes so that their blood levels could be tested periodically and analyzed for lead content (Adams 2002, at 1044-1045). The participants were required to sign a consent form indicating their willingness to participate in the study as well as their intent to remain in the premises for a minimum of two years, the length of the research study. Exclusion criteria included mental retardation, physical handicaps, and sickle cell anemia. Parents gave permission to enroll their children and agreed to have eight to nine blood tests over the two-year period as well as to have their homes tested for lead a similar number of times (Beh 2002, at 7). Nowhere did the consent form indicate the risks and health dangers lead paint posed to

children or the possibility of developing lead poisoning, which impairs cognitive and physical development, as a result of the study (Id.).

The research study protocol ultimately had IRB approval. As the study was first proposed, the IRB expressed concerns regarding the use of healthy control children in modern urban housing. The IRB was concerned that the federal regulations did not allow this non-therapeutic use of healthy children in the study, in particular, in drawing blood from the control population (Beh 2002, at 7-8). The IRB suggested revisions to the consent form so that the healthy control group children were not submitted to blood tests with no anticipated benefit. The IRB suggested changing the form to indicate that the healthy children would be tested to determine what role exposure outside the home may play in total lead exposure and whether living in safe housing, alone, is enough to keep blood lead levels in acceptable bounds. Eventually the IRB approved the revised consent form that reflected that all children would receive certain benefits (Id.). The IRB -approved consent form further explained that besides compensation, KKI would provide the parents with specific blood-lead level results and would discuss the lead levels found in testing the housing. KKI also agreed, in the consent form, to discuss with the parents ways they could help guard against lead exposures (Id.).

In March 1993, ten- month old Ericka Grimes was recruited into the study. KKI representatives visited Viola Hughes, Grimes' mother, to discuss the purpose, nature,

scope and benefits of the study. Hughes agreed to allow her daughter to participate and signed the consent form. The form did not disclose that Erika could accumulate dangerous levels of lead in her blood during the study (Adams 2002, at 1046). Of note, some children in the study, like Erika Grimes, were already living in the housing to be studied but some families were actually moved into the contaminated properties during the study. Some of the properties had been abandoned and were vacant until the landlords were approached to participate in the study and even agreed to rent their properties to families with young children (Beh 2002, at 6-7). KKI collected dust samples from the Grimes home several times using an experimental method of capturing dust through the use of a cyclone vacuum as well as the traditional dust wipe method. In addition, it collected exterior soil and drinking water measurements. The first dust sample from March 9, 1993 revealed “hot spots” in the home. However, information about the sample was not provided to Hughes until almost ten months after the sample had been collected (Adams 2002, at 1046-47). Blood samples were also collected from Erika Grimes. The results of the first blood test showed her blood lead level to be within the normal range. However, two subsequent tests showed her levels to be highly elevated. These elevated levels came after KKI identified the hot spots in the home but before it advised Hughes of the dangerous lead levels. Hughes and Erika subsequently vacated the premises in the summer of 1994 and no further testing was done (Id.).

Thereupon, Viola Hughes filed a complaint in the Circuit Court for Baltimore City alleging that KKI was negligent for failing to warn of the lead paint hazards that it had

discovered. KKI moved for summary judgment on the grounds that it did not owe a duty to Grimes. The Circuit Court granted KKI's motion finding that no special relationship existed between KKI and Grimes that imposed a duty on KKI. Grimes appealed. As we know, to establish negligence there must be (1) a duty (2) that has been breached (3) resulting in damages (4) proximately caused by the breach. Without a duty, there could be no negligence. On appeal, Grimes contended that, despite the Circuit Court ruling, KKI did owe a duty and by not advising of the elevated, unsafe levels of lead in the home for at least ten months after it was discovered, that duty was breached. Grimes' argument was based, at least in part, on the claim that a special relationship existed between KKI and Grimes and that the danger posed by lead paint was foreseeable (Adams 2002, at 1050). Grimes also contended that KKI had an affirmative duty to give complete and accurate information concerning the risks and hazards of participating in the study, something allegedly missing from the IRB-approved consent form. The Court of Appeals of Maryland considered whether a special relationship exists between a research institute and a human subject on three bases: whether the informed consent is a document that can be deemed a contract establishing a special relationship; whether the very nature of human subject research creates a special relationship, and whether federal regulations create duties that researchers owe to human subjects out of which a special relationship may arise (Adams 2002, at 1061). The Appeals Court vacated the lower court decision and remanded the matter for further consideration on whether a special relationship existed. The only real ruling of this court was that summary judgment was inappropriate. On remand, although concerns were raised about the adequacy of the informed consent process and the timeliness of informing the parents of the lead levels in

the housing, the case was eventually dismissed without prejudice by the lower court (Buchanan and Miller 2006, at 782).

Despite this, the most important part of the Appeals Court ruling was a general discussion on the subject of using humans for research and its far-reaching criticism of the IRB. In fact, Judge Cathell, writing for the majority, issued a scathing 96- page opinion, beginning with Nuremberg, then discussing Gelsinger and other research experiments. The judges called the lead paint study a callous scientific experiment that put children in harm's way, saying the children were merely being used as measuring tools (Buchanan and Miller 2006, at 782). To begin with, the Court found that the consent form, though revised, was not well drafted and did not adequately inform. Furthermore, the Court harshly criticized the IRB's involvement in labeling health monitoring as a benefit, explaining, "The IRB abdicated that responsibility, instead suggesting to the researchers a way to miscast the characteristics of the study in order to avoid the responsibility inherent in non-therapeutic research involving children" (Beh 2002, at 9-10). The Court also concluded that the IRB had at least a partial misconception between therapeutic and nontherapeutic research and the IRB's role in the process of approving research. It asserted that the IRB misconstrued its role in protecting subjects by helping researchers to circumvent the federal regulations and found that there was no therapeutic value to the healthy control minor subjects (Id.).

As can be imagined, there was strong reaction to the court's ruling. There was widespread concern among researchers with respect to the part of the ruling finding that children should not be included in research trials that do not have a therapeutic benefit and which include risk (Spriggs 2004). The court maintained that the lead paint study was a nontherapeutic research program and ruled that a parent cannot consent to the participation of a child in nontherapeutic research or studies in which there is any risk of injury or damage to the health of the subject (Spriggs 2004, at 176). Critics of this ruling were quite vocal, alleging that if left unchallenged, the ruling would stop valuable research and could do immeasurable harm to all children (Spriggs 2004, at 177).

It is notable that the Maryland court delved into an area that had been considered and rejected by the National Commission, the distinction between therapeutic and nontherapeutic research. It was also one of the issues in the debate over revisions to the Declaration of Helsinki and was dropped from the revised Declaration in 2000 (Id.). However, this distinction and its ramifications are beyond the scope of this paper. It is the court's clear denunciation of the methods used by the Hopkins IRB in getting the researcher to revise the consent form that is of interest here. The IRB tried to have participants give consent to a study that involved no risk at all or at least no increase over minimal risk. The crucial question in the IRB review was whether the continued exposure to lead should be considered a risk of the study or just part of everyday life since it was part of the living conditions of the children. The IRB's perception of risk was the blood draws, not the lead exposure, which was part of the nature of living in old

housing in Baltimore (Id.). This account of the IRB's rationale was not given much credit by the Maryland court. The court found that the IRB approved consent form did not contain information a reasonable parent would want to know, including nothing about the importance of monitoring lead levels and the risks posed by elevated levels. Rather, the consent form seemed to entice parents with free testing of dust, soil, water and blood as well as with trinkets, food stamps, money and other items (Spriggs 2004, at 178).

The Belmont principles and resulting federal regulations focus on individual protections, without explicit attention to community level protections. In fact, in 1999 bioethicist Charles Weijer suggested that a fourth ethical principle should be added to those found in Belmont: the principle of respect for communities (Weijer 1999). In 2001, the National Bioethics Advisory Commission proposed regulatory oversight for not only individual human subjects but also for the protection of social groups. Considering community groups in connection with human subject research brings new and different ethical dimensions to bear. Community level risks and benefits may be different. Community groups, for instance in the Baltimore lead paint KKI study, may have identified risks unforeseen by or in addition to those apparent to the IRB. The risk to children in the KKI study included those resulting from exposure to lead as well as those relating to the blood draws. On one hand, the community risk could be that residents will exit neighborhoods with the stigma of elevated risk of lead exposure and such neighborhoods will become blighted and uninhabitable. On the other hand, the study could potentially

be a benefit to such a neighborhood by bringing attention and possibly funding for lead abatement, making it attractive to residents.

The IRB that reviewed the KKI protocol could have done a better job of including the community in its ethical review. The community members could have been involved in ensuring that the participants' parents understood the research to be conducted and the consent process, as well as the consent form itself. Community members with a working knowledge of housing health hazards could have been used as consultants to the IRB or could have been part of a community advisory board for the research. The KKI lead paint study provided the perfect opportunity to engage community members in the review and approval process in balancing the individual protections with the benefits to be obtained for the public in general and this community in particular.

3. The Case of Ellen Roche

At about the same time as the lead paint study discussed above, a healthy, young research assistant participating in a clinical trial died after inhaling an unapproved drug as part of a study into the causes of asthma. Twenty-four year old Ellen Roche worked at the Johns Hopkins Asthma and Allergy Center beginning in 1999. Roche had previously participated in several studies conducted by researchers at the Center when, in 2001, she signed up to participate as a normal volunteer in an asthma study protocol designed by Dr. Alkis Togias. The study was designed to investigate whether normal individuals can

reverse airway constrictions caused by various irritants by taking deep breaths where individuals with asthma could not. One of the drugs used in the study was hexamethonium, a blood pressure medication previously removed from the market by the manufacturer after the FDA declared it ineffective. Participants were to inhale the chemical so that researchers could see how their lungs responded to the irritant. The first participant developed a dry cough, which abated in about a week. The second subject apparently suffered no ill effects. When Ellen Roche was given the medication, she developed a dry cough that did not abate and her condition deteriorated so that she was admitted to intensive care about five days after receiving the chemical and died on June 2, 2001, within a month of inhalation of hexamethonium (Keiger and DePasquale 2001).

The study in which Roche participated was part of a National Institute of Health funded study. Dr. Togias was the co-investigator on the grant and in charge of the study at Hopkins. The particular administration of hexamethonium was not part of the original study application but was submitted later and was ultimately approved by the Johns Hopkins Bayview Medical Center IRB (Id.). One important aspect of the IRB approval of the use of hexamethonium needs to be considered. The drug had several serious side effects. The label for hexamethonium tablets marketed by Richlyn Laboratories of Philadelphia warned of fainting, blurred vision, among other effects. Several articles in medical journals in the 50s and 60s warned of prolonged use of the drug, which could lead to inflammation of the lungs. The drug was never approved in the inhalation form.

In 1971, the FDA ruled the drug was ineffective and it was withdrawn from the market. The JHU IRB approved Dr. Togias' protocol believing his presumption that the drug was safe at lower doses. Togias based his presumption on a computer data search for adverse effects of the drug using PubMed and finding no indication of lung toxicity (Id.). Dr. Togias' literature review has been severely criticized for its lack of breadth, for not being extensive and for not being an effective search on hexamethonium and its toxicity. Commentators have noted that a qualified medical librarian, familiar with biomedical and pharmacological information, would have known such things as date limitations on PubMed (mostly only back to 1966), would have been more familiar with search-term conventions and would have been less likely to miss valuable, life-saving information (Miller 2009). Actually, Miller discusses how one can determine if adequate preliminary research has been done and calls to mind Donald Rumsfeld's famous quote: "There are known knowns. There are things we know that we know. There are known unknowns. That is to say, there are things that we now know we don't know. But there are also unknown unknowns. There are things we don't know we don't know" (Id.). That last category is, by far, the most problematic, particularly in the context of ethical human subject research.

The federal agencies with oversight and jurisdiction over human experimentation reacted quickly to the report of the death of Ellen Roche. The FDA inspectors provided their preliminary findings to Dr. Togias by June 28, 2001 and made them public July 2, 2001. Basically the FDA found four violations: failure to obtain an investigational new drug

application for hexamethonium; failure to report unanticipated adverse events in the first volunteer to receive the drug; failure to follow the research protocol as approved, and failure to obtain informed consent by not informing the volunteers that hexamethonium was not FDA approved and inhalation of this drug was experimental. (Medico Legal Consultants) The OHRP then shut down all human research at Hopkins in July 2001 after its investigation and before Hopkins itself instituted its own external review committee investigation. Hopkins was embarrassed and, claiming its system was superior to other research institutions, blamed bureaucratic overzealousness of the regulators. However, Hopkins quickly took corrective action and the suspension was lifted after just 4 days (Id.). Hopkins did accept full responsibility for the death of Roche. The University further reported that the researcher who conducted the experiment and the ethics committee that approved it failed to take adequate precautions to protect research subjects (Kolata 2001). In fact, Dr. Togias had represented to the Hopkins IRB that the main risk of hexamethonium was a drop in blood pressure. His conclusions were reflected in the consent form that was approved by the IRB and that Roche signed (Id.). The form should not have received IRB approval, as it did not mention that hexamethonium was not FDA approved and did not say that the drug's safety was uncertain. The external review committee investigating the incident concluded that the IRB should have required more evidence of safety in the use of hexamethonium (Id.). Aside from the problems directly related to Dr. Togias and the research protocol involving Roche, the committee found numerous problems with the entire IRB supervision of research protocols, calling it grossly inadequate and not conforming to current standards (Medico Legal Consultants). The most significant

problem identified was the absence of any discussions of protocols by the entire board. Apparently, individual IRB members reviewed and presented protocols to the board. Several research protocols were voted on at once with approvals routinely given (Id.). There was no group discussion of Dr. Togias' proposal, thus defeating one of the primary goals of IRB review, obtaining a consensus of knowledgeable professionals from various fields to avoid unknown pitfalls in a research protocol (Id.). Thus, the Hopkins IRB thwarted the main purpose of IRB review under the federal regulations.

By August 2001, Hopkins published a document entitled: "Actions Taken to Strengthen Research Oversight at Johns Hopkins" (hopkinsmedicine.org 2001). Significant new safeguards endorsed by the federal government and by an external review committee were put in place to protect the safety of those who participate in research. Some highlights of the new procedures include: expand the number of IRBs; intensify training for all IRB members; implement the full convened IRB meeting review process to ensure full board review, discussion and documentation of each protocol; require researchers to collaborate with a librarian and pharmacist to strengthen literature searches; establish a policy of seeking IND status in all instances when a non-approved substance is specified in a protocol, and increase random quality control checks of ongoing research (Id.). Hopkins further noted that it recognized the need for increased long-term education at all levels of the institution to ensure a full appreciation of the ethical obligations inherent in research involving humans (Id.). Despite its blustery denunciation of OHRP and its presumed regulatory overreach, Hopkins took the entire

Roche situation very seriously and reacted quickly in its efforts to meet or exceed the federal regulatory requirements.

D. Pros and Cons of IRB Review

The three examples above would seem to provide indisputable evidence that the current system for review of human subject research is flawed. Some might say that IRB review is based too much on procedures and not enough on ethical principles (Stark 2012). IRB review had its genesis in the Clinical Research Committee, a group of leaders of the Clinical Center of NIH who would collectively endorse research deemed to be acceptable or restrict research not deemed so (Stark 2012, at 2). It was in this context that NIH devised the concept of group consideration of research by those uninvolved in the actual research protocol. It was in 1953 that the surgeon general of the Public Health Service formally endorsed group consideration as the practice that would ensure upstanding research at the NIH Clinical Center (Stark 2012, at 109).

Furthermore, and as discussed above, IRBs are not governmental agencies. IRBs derive their power from the regulations but the power is given to IRBs, not to individuals. Thus, IRBs, like their NIH predecessors, can act only by consensus. Individuals are not empowered to act. My personal observation of IRB meetings affirms that the members were quite congenial and cordial to one another. Collegiality reigns. Board members are assigned specific protocols to review, including the proposals, consent forms,

recruitment fliers and the like. Each board member then reports out on the assigned protocols at the meetings. There was little confrontational or adversarial type discussion in the meetings I attended and basically all votes on research protocols were unanimous, most being approved either as presented or with recommended modifications. There was very little challenging of a reviewer's recommendations. It seemed that each IRB member recognized and deferred to the expertise of the one member presenting on a particular protocol.

E. Criticisms of IRBs

It is easy to find repeated instances in research ethics literature where commentators acknowledge shortcomings of IRBs. They are often referred to as too weak, overburdened, ignorant, or conflicted to adequately perform the important duties the federal regulations impose (Beh 2002, at 34). In fact, the oft-cited 1998 report of the Office of Inspector General (OIG) specifically warned that the effectiveness of IRBs is in jeopardy, with their resources strained by the number and complexity of research proposals. The OIG report found that IRBs review "too much, too quickly, with too little expertise" (Id.). The OIG importantly also found that the effectiveness of IRBs has not been subject to critical evaluation, with too much attention focusing on perfunctory review rather than on human subject protections. This concept of IRB review resounds in Stark's recent work cited above. Is it a fair criticism that IRB review is so heavily administrative that ethical principles are lost in the shuffle? On the other hand, is the real question: Can an IRB really perform the dual role of protecting human

subjects while promoting the pursuit of scientific knowledge? The issues raised by these questions are addressed in ensuing chapters of this thesis.

One popularly cited shortcoming of IRBs centers on the fact that IRB members are typically researchers themselves, drawn from the institution conducting the research, with the very real possibility of inherent biases favoring the conduct of research. IRBs must perform their oversight responsibilities within the environment, including the culture and pressures, of that research institution. It is really a type of self-regulation (Gatter 2005). Gatter proposes that a possible solution to this problem is to establish a centralized review process, thereby creating greater efficiencies and allowing for greater expertise. This, however, is not without its own problems. For example, local and/or regional variations would not be as easily incorporated, with the result that local community norms might not be taken into account in the protocols (Gatter 2005, at 620). Beyond the central oversight alternative is one used in France whereby research protocols are reviewed by freestanding local ethics committees appointed by the local government rather than by those affiliated with the research institution (Id.). This approach allows a measure of independence to the reviewers while at the same time allowing local community interests to be considered. Regional review boards, unaffiliated with the research institutions, are also used in the UK. The downside to using reviewers outside the institution is the potential for a more adversarial relationship between researchers and reviewers.

Another frequent comment on IRBs is the lack of sufficient training in the substantive topic of ethical research involving human subjects, including such aspects as informed consent or an in-depth understanding of the federal regulations (Beh 2002, at 35). Often IRB members are offered only minimal training, mainly the on-line CITI course. The lack of more substantive ethical and regulatory training is seen as a fundamental flaw, which impedes an IRB's performance. It is also noted that training is needed as a counterbalance to the interests or biases of the principal investigator or the institution in seeing that the research is performed (Beh 2002, at 36). While charged with protecting research subjects, the IRB is part of the institution seeking to obtain regulatory compliance so that funding is not jeopardized.

Perhaps the most crucial purported shortcoming of IRBs is that they pay too much attention to the niceties of the consent forms and do not consider the risk-benefit assessment portion of their charge (Coleman 2004). It is the risk assessment aspect of IRB review that is the focus of an article by Coleman. Coleman compares the IRB process of decision-making with the legal process of decision-making, hypothesizing that both IRBs and courts interpret specific regulatory requirements pursuant to authority that is delegated to them by administrative agencies (Coleman 2004, at 4). Coleman is a proponent of casuistry in the IRB review process. In fact, he goes so far as to suggest that a jury type system may do a more effective risk assessment than IRBs, as currently constructed (Coleman 2004, at 19). Coleman makes the case that IRB review is, on the whole, inadequate, since IRBs are overburdened, underfunded, insufficiently

prepared, and often too willing to rely on investigators' good intentions as the primary method for protecting subjects. Another concern is that very little substantive review takes place at convened meetings and that there is little evidence that IRB approval of research is consistently based on considerations required by the regulations. All in all the result is unreasonably risky research (Coleman 2004, at 11). Opportunities for systemic reform of IRBs and their operations are considered in later chapters of this thesis.

CHAPTER 3

A. HHS Proposed Overhaul of Human Subject Protections in Research

On July 26, 2011, HHS, in coordination with the Office of Science and Technology Policy, published an advance notice of proposed rulemaking entitled “Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay and Ambiguity for Investigators” (DHHS 2011, at 44,512), (ANPRM). The stated purpose of the ANPRM was to solicit comments in order to identify ways to better protect human subjects who are involved in research, while facilitating valuable research and reducing burden, delay and ambiguity for investigators (Id.). The ANPRM is to amend 45 CFR Part 46, Subpart A, also known as the Common Rule. Comments were originally due by September 26, 2011, with that date subsequently extended.

The Office of Human Research Protections (OHRP) issued a statement on its website indicating that it will use the comments received from interested stakeholders in response to the ANPRM in order to develop the proposed new regulations. As of this writing, the comment period has finally closed and the Notice of Proposed Rulemaking (NPRM) was due April 2013, with an additional comment period to follow. It has not been issued. The ANPRM proposes an expansion of the jurisdiction of the Common Rule as well as a wide-range of significant substantive and procedural changes. The ANPRM could have a profound effect on the ways in which human subject research is conducted. It would

probably require that research institutions make meaningful operational and compliance changes in their research programs (Geetter 2011). Although OHRP has issued a series of guidelines over the years to clarify the Common Rule's requirements and to address emerging compliance issues, the rule itself has not undergone significant revisions since 1991. HHS acknowledges that the "landscape of research activities has changed dramatically" and there are valid questions about whether the current regulatory framework is adequate and appropriate for the protection of human subjects in the 21st century (DHHS 2011, at 44,513).

HHS offers two broad motivations for its current efforts to update the Common Rule: to address dramatic changes in the research landscape over the past two decades and to improve the effectiveness and efficiency of the Common Rule in light of the current research environment. HHS suggests seven broad categories of changes to the Common Rule: (1) Refinement of the existing risk-based regulatory framework; (2) Utilization of a single IRB review of record for domestic sites of multi-site studies; (3) Improvement of consent forms and the consent process; (4) Establishment of mandatory data security and information protection standards for all studies that involve identifiable data; (5) Establishment of an improved, more systemic approach for the collection and analysis of data on unanticipated problems and adverse events; (6) Extension of Federal regulatory protections to all research, regardless of source of funding, conducted at institutions in the U.S. that receive some Federal funding from a Common Rule agency

for research with human subjects; and (7) Improvement in the harmonization of regulations and related agency guidance (DHHS 2011, at 44,514).

The ANPRM then sets forth proposed recommendations to address each of these areas with comments requested on specific questions (DHHS 2011, at 44,529). There are a total of 74 distinct questions, and commenters are asked to address these specific questions as well as to provide general feedback on the current regulatory scheme. Each of the seven categories is addressed in detail below.

HHS proposes to extend the Common Rule to research that is not federally funded but which is conducted at a U.S. institution that receives some funding for human subjects research from a Common Rule federal agency (DHHS 2011, at 44,528). Already, many institutions voluntarily extend the Common Rule to all non-federally funded research via election of the OHRP-approved Federal Wide Assurance (FWA), but not all institutions so elect. This is actually a reversion back to certain aspects of earlier forms of assurance. Prior to December 31, 2005, two types of assurances covered all research, whether receiving federal funds or not, if conducted at a U.S. institution receiving any monies for human subject research from a Common Rule federal agency. A single project assurance was given to cover one grant or project. Multiple project assurances were given to cover all research at an institution. The older forms were seen as complex and arcane (Charrow 2007). In fact, just prior to the July 2011 publication of the

ANPRM, OHRP announced a revised FWA form and process applicable to institutions participating in federally funded human subject research activities. Announced on June 20, 2011, the changes focus on the designation by institutions of IRBs charged with reviewing research.

Previously, an institution was required to designate each IRB used, both internal and external, as a supervising IRB for human subject research subject to the Common Rule. Institutions were also required to submit updates to OHRP when the institution wished to rely on a previously undesignated IRB. An example of the burdensomeness of this requirement is the situation where a multi-site study would be overseen by a centralized IRB. An institution participating in the study would first need to update the FWA to include the new IRB. The new FWA application only requires the designation of all internal IRBs and only one external, even if multiple external IRBs are used. Despite the more relaxed rule, institutions are still required to use IRBs on OHRP's list of approved IRBs for oversight of any federally funded studies or for all studies if such election is made.

ANPRM seeks comments on the current and proposed risk-based regulatory framework for human subject protections based, at least in part, on the concern that concepts of "minimal risk" are misunderstood and inappropriately applied by IRBs. The proposal states that, "the concern is that IRBs spend too much time reviewing minimal risk

research... and overestimate the magnitude and probability of foreseeable risks” (DHHS 2011, at 44,515). Suggested changes in this area include eliminating continuing review for minimal risk research that receives expedited IRB review, and revising and regularly updating the expedited review categories with an eye to expanding the types of minimal risk research that can undergo expedited review. Another suggestion is to have researchers register their exempt studies and allow the research to commence immediately upon registration rather than after IRB review of the exempt status, with continuing IRB review not required or even recommended. This would be monitored by random, retrospective audits to assess whether exempt status was appropriately applied. Proposed expanded exempt categories would include such studies as those involving tests, surveys, interviews and similar procedures so long as the subjects are competent adults. Further, a new category of minimal risk research would be added for behavioral and social science research that goes beyond the current survey only methodology (Id.).

Minimal risk research categories would also be extended to all secondary research using identifiable data and biospecimens collected for purposes other than the research at hand. Data security standards for identifiable information would need to be established as well as for de-identified information, consistent with the level of risk (DHHS 2011 at 44,526). The term exempt would be changed to “excused” under the proposed regulations. The “excused” studies would probably be excused from IRB review, but would still be subject to the data security and information protection standards and, in some cases, informed consent requirements. It will be interesting to see how consent requirements square with

no IRB review in practice and whether consent requirements are appropriate for research on de-identified, previously existing biospecimens obtained without a waiver, and whether pre-existing data should be treated differently than pre-existing biospecimens.

The changes suggested above to the risk-based regulatory framework would affect the education and training of IRB members and investigators with regard to ethics and, in particular, the concepts of minimal risk and non-medical human subject research. There would potentially be a reduction in the workload of IRBs for continuing review, as expedited studies would no longer require such ongoing monitoring. IRB submission processes would need to be modified, as expedited and exempt studies may not need to be submitted. However, there would need to be a process developed for the registration of such studies and for consideration of consent documents. It will be interesting to note, if these changes do become the rule, whether IRB workload will truly decrease and what types of risks may potentially slip through the cracks.

HHS acknowledges the growth in utilization of multiple sites to conduct human subject research and suggests streamlining IRB review of these multi-site studies (DHHS 2011, at 44,521). To address inefficiencies placed on multi-site studies due to review by multiple IRBs, the suggestion is to mandate that all domestic sites in such studies rely on a single IRB as the IRB of record for the study. The hope is to reduce workloads and start-up times for research and to minimize conflicts of interest by eliminating the need to

submit for local review and approval with possibly different levels of review and different outcomes. The proposed mandate would also include changes to enforcement procedures that will hold external IRBs directly accountable for regulatory compliance so that institutions can rely on them in relation to the conduct of the approved research. The requirement for a single IRB of record does not prohibit individual sites from conducting additional internal ethics reviews. Of note, however, local IRBs would still have accountability for the protection of human subjects at their institutions and studies involving FDA regulated devices would still need local IRB review consistent with FDA regulations. Centralized IRB review would apply only to domestic multi-site studies. Issues presented would seem to include: how the IRB of record would be selected, especially in light of the desired goal of avoiding forum or IRB shopping; whether a central IRB would have adequate knowledge of each site, and whether a central IRB could adequately address liability concerns at each site involved in the study. Another issue to be considered is whether a local IRB would have any ongoing responsibility for a study once it has been approved by a central IRB. Does any liability the institution faces in connection with the study militate in favor of a local oversight body or does the central IRB have sufficient resources to oversee the study at each of the multiple sites?

The ANPRM also takes up the issue of improving the informed consent process for human subject research (DHHS 2011, at 44,522). Consent forms are often criticized as being overly long, too complicated, difficult to understand and missing important information related to the study risks. IRBs typically spend considerable time reviewing

consent forms with much attention to procedural requirements and possibly not enough attention to substance and readability, which often exceeds the desired 8th grade level. In fact, the ANPRM states that consent forms have become excessively long and legalistic, even for routine or relatively low risk studies. Six modifications to consent forms have been proposed, including: prescribing specific content that must be included; restricting inappropriate content; limiting acceptable length; prescribing how information is to be presented; reducing boilerplate serving only to protect the institution and not the subject, and providing standard consent form templates. In addition, the ANPRM describes two other areas of concern with respect to the informed consent process: the vagueness and non-standard application of criteria for waivers, and the rationale for requiring a signed consent for the research use of specimens.

As for the consent for use of specimens issue, this seems to be based, at least in part, on HHS' interpretation of the Health Insurance Portability and Accountability Act (HIPAA) rules that require authorizations to be study specific. Furthermore, it seems that HHS believes it is inappropriate to obtain global authorizations for unspecified future research. It is argued that both the Common Rule and the HIPAA Privacy Rule should be aligned to allow subjects to object to the use of their biospecimens in research. Without a consent requirement, this purpose would be frustrated. However, the converse is also true: that investigators are concerned about logistical difficulties in obtaining consent for each specimen study when the specimen already exists and about the potential negative impact if significant numbers of specimen providers refuse consent. Thus,

HHS seeks to clarify criteria for waivers of informed consent and for oral consent as well as to clarify circumstances under which future research use of data would or would not require informed consent.

In the realm of data security and information protections, HHS proposes that the Common Rule incorporate standards enunciated in the 1996 Privacy and Security Rules Act, as part of HIPAA to, first of all, define identifiable information and de-identified information. HHS could evaluate and supplement these definitions as necessary for its purposes. Specific data protections would be modeled on the HIPAA Security Rule and would include administrative, physical, and technical safeguards, as well as data breach notification procedures (DHHS 2011, at 44,524). HHS proposes establishing mandatory data security and information protection standards for all research studies that involve identifiable and potentially identifiable data and in which data is collected, stored, analyzed or otherwise reused. HHS also proposes establishing a web-based, federal-wide portal that would allow the electronic submission of certain safety data with automatic distribution to the appropriate agencies and oversight bodies in order to simplify and consolidate the reporting of such data. Importantly, with these new rules, HHS expects to streamline the IRB process and no longer require the IRB to assess the adequacy of the protections against informational risks. The rules would further provide for retrospective, random audits and additional enforcement tools for the agencies.

Seventh, HHS proposes harmonizing various regulations and related guidance among the agencies that have adopted the Common Rule (DHHS 2011, at 44,528). It has long been thought that uniformity is desirable among departments and agencies to eliminate unnecessary regulation and to promote increased understanding and ease of compliance by institutions that conduct federally supported or regulated research involving human subjects (Id.). Each of the 15 departments and agencies adopting the Common Rule, however, is allowed to issue its own guidance documents for applying the strictures of the Rule tailored to that agency's specific needs and requirements. In addition, other federal laws exist for the protection of human subjects; for instance and as already discussed, the HIPAA Rules and regulations promulgated by the FDA. The combination of these factors has led to research involving human subjects' being subject to inconsistent and sometimes contradictory regulatory schemes. In this area, the ANPRM has not proposed a specific change but rather has requested comment on whether differences in guidance documents among the agencies are justified or, if not, on how to make guidance more uniform, eliminating the unnecessary differences.

As has been set forth in some detail above, the ANPRM sets out a series of changes designed to expedite the research review and oversight process, for example, expanding the categories of exempt or excused status and eliminating continued review of appropriately characterized minimal risk studies. In many respects, the ANPRM seeks to relax provisions of the current Common Rule to improve efficiency and remove burdens on investigators that do not, in HHS' view, meaningfully add to human subject

protections. However, a few of its proposed changes add to or strengthen aspects of the current Common Rule; for instance, extending compliance with the Common Rule for all research studies at any institution receiving federal funding for research. Although the ANPRM covers a broad array of concerns relating to human subject research, there are certain issues contested in the research community that are not addressed. The ANPRM does not, for instance, provide direction on what constitutes exculpatory language in informed consent forms, which language has created confusion and ambiguity in subjects' understanding of the institution's responsibility relating to research risks. Another example is that the ANPRM does not address the issue of conflicts of interest or the role of data and safety monitoring boards. It seems that some inconsistencies among agencies covered by the Common Rule will exist despite HHS' efforts. There is also the potential for unintended consequences once the changes are effectuated; in practice ambiguities may and probably will arise. All that being said, these are somewhat sweeping changes for a regulation that has not undergone meaningful revision in over two decades, despite the rapidly changing world of human subject research it is trying to contain. Given the long list of questions presented for comment in the ANPRM, it is not surprising that the comment period was extended and that large numbers of stakeholders have responded.

B. Overview of Certain Comments to the Proposed Changes to the Common Rule

In this section, I attempt to capture some of the comments provided by stakeholders relating, for the most part, to how the use and functions of IRBs will be affected by the

proposed rule changes. It is not possible to actually segregate those changes related specifically to IRBs since there is a significant overlap in the proposals. In addition, due to the vast number of responses submitted to the ANPRM (at least 1100), I have elected to focus on the following two categories of respondents: (1) academia; and (2) those affiliated with IRBs.

As representative of academia, I discuss the comments submitted on behalf of the Association of American Medical Colleges (AAMC) by its Chief Scientific Officer, Ann Bonham, on October 25, 2011, and the individual response of a private university, Yale, submitted by the University General Counsel, Dorothy K. Robinson on October 26, 2011. Comments of Joan Rachlin of Public Responsibility in Medicine and Research (PRIM&R) submitted on October 26, 2011 and the October 7, 2011 comments of Marjorie A. Speers on behalf of the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) will be presented as representative of those entities concerned with IRBs. I end this section with a few general comments obtained from an “ANPRM: Summary of Comments” compiled by Edward E. Bartlett, PhD, Office for Human Research Protections, dated February 24, 2012. While not an official document of OHRP and reflecting only the views of the author, this summary is helpful for a broad perspective look at how the stakeholders respond to the ANPRM.

It will not be surprising to see that each of these constituencies addresses the proposed changes from its own unique perspective and each focuses on the potential impact on its own research world. As stated, there is significant overlap among the seven broad categories of proposed changes, so that objectively examining only those dealing with or affecting IRBs is difficult. However, in order to look more closely at the proposed rule changes from an effect on IRB perspective, I have selected the following broad categories of changes to examine: (1) informed consent; (2) centralized IRBs for multi-site studies; (3) alignment of risk level with review level, and (4) the requirement of written consent for research use of all biospecimens. It is perhaps the exempt status revisions and the proposals relating to biospecimens that are the central and most important of the proposed changes to the Common Rule, with the greatest far-reaching future impact.

1. Academia

AAMC

It should be noted at the outset that AAMC is a not-for-profit organization representing 135 accredited U.S. and 17 accredited Canadian medical schools; nearly 400 major teaching hospitals and health systems, and nearly 90 academic and scientific societies. (AAMC comments to Docket Number HHS-OHRP-2011-0005)

a. AAMC agrees that informed consent documentation can and should be improved. Specifically, AAMC finds the current consent forms are generally used only as communication tools, proof of regulatory compliance, shields against liability, and catalogues of extraneous information (AAMC comments, at 10). A position that appears fairly constant throughout the comments reviewed posits that the current consent forms dilute the fundamental goals of the consent process itself, which should focus on providing individuals the relevant information, time to review, and the opportunities to ask questions to ensure that the consent is truly voluntary and truly informed. AAMC agrees that consent forms should be shortened and simplified but does not agree that specific page limits are needed, or that other proscriptive formatting requirements are appropriate. AAMC supports guidance on consent forms rather than templates so that institutions have flexibility and the proposed templates do not take on the importance of regulations (AAMC comments, at 11).

b. AAMC seems to agree in principle to the mandate of a single IRB for multi-site research studies, but cautions that the process of mandating this change needs to be deliberate and thoughtful (AAMC comments, at 9). AAMC believes OHRP has more work to do on this issue before enacting such a change. One caution of note relates to preventing the development of “shadow” local review systems designed to protect against real or perceived institutional liability or risk of enforcement actions. Further, AAMC opines that the Common Rule already allows for central IRBs, so really no changes in the regulations are needed, just guidance. Guidance is particularly needed in the areas of

defining what specifically is a multi-site study, how is a central IRB selected, defining clear roles and responsibilities for the central IRB, and giving due consideration to the local context, that is, community specific needs and challenges (Id.).

c. AAMC sets out several comments relating to calibrating the degree of IRB oversight with the degree of risk to human subjects. First, AAMC agrees with eliminating mandatory annual continuing reviews for research that qualifies for the expedited review process. Second, AAMC supports eliminating annual continuing review for studies posing greater than minimal risk once all remaining activities would be eligible for expedited review or would be exempt from the regulations. It should be within the authority of the IRB to decide when research has reached the eligibility threshold to discontinue ongoing review. However, flexibility must also be built into the Rule to allow IRBs to determine when more frequent review is necessary (AAMC comments, at 5). AAMC also agrees that IRBs should have the flexibility to modify or waive certain criteria required for expedited review, and further supports the proposal to review and update the list of research activities eligible for expedited review (Id. at 6).

AAMC appears emphatic in its disagreement with the ANPRM section on changes to the exempt category. AAMC rejects the use of the word “excused” and believes that it is inappropriate to shift the decision on whether a research protocol falls within the exempt category from an IRB member to an investigator. AAMC opines that, even with clear

definitions and guidance, there exists the potential for an investigator to err or to misclassify research as excused with the risk of exposing human subjects to harm (Id. at 7). Furthermore, AAMC believes that mandating audits after excused research has already begun, or possibly is already completed, does not provide adequate protections and only serves to increase burdens on investigators, IRBs and institutions. Open questions relating to audits include discussing how audits of excused research would be conducted, and what would be the responsibilities of sponsors or institutions if problems are found either in the registration or in the conduct of the research.

d. AAMC believes that, with regard to data and biospecimen research where the identity of the source cannot be readily ascertained, it would be an unnecessary burden on important research to impose requirements as proposed for the new “excused” category. These administrative requirements would not meaningfully add protections to individuals from whom such information and materials derive. AAMC believes it is preferable to keep these outside both the historic definition of human subject research and the current regulatory scheme (Id. at 8). AAMC also supports maintaining the current regulations for protections and waivers for identifiable data and biospecimens, since they work appropriately to balance subject protections against researchers’ burdens.

YALE

a. Yale agrees (as do all commentators reviewed) that most informed consent forms are too lengthy and complex. Yale supports the creation of a summary, two-page or so document to be signed by the participant that would describe the research in clear, concise language, with its risks, benefits and alternatives to participation. Accompanying this short document would be a fulsome appendix (Yale comments, at 3,4) Yale, like AAMC, opposes the use of templates as these can take on the force of regulations over time. OHRP should provide guidance but allow institutions flexibility in consent documents, as the ultimate responsibility resides in the institution.

b. Like AAMC, Yale supports the use of a single IRB for multi-site studies but suggests that a number of issues require additional attention before duplicative reviews are eliminated and the goal of improved protocol review is achieved. Primarily, the roles and responsibilities of the central and the local IRBs must be clarified, especially as they relate to local context considerations (Id.). Yale believes that if the NPRM moves forward with this mandate, a tiered approach should be used, at first limited to established central IRBs, for instance NCI's.

c. Yale supports efforts to calibrate type of review to level of risk posed by a research study, with an established minimal standard of risk and institutions granted the flexibility to determine a level of review and continuing oversight commensurate with the study's degree of risk. Yale further supports eliminating continuing review requirements for

minimal risk studies but wants IRBs to be able to establish local standards for reporting progress on minimal risk studies (Id. at 2). Yale seems to agree that the proposed “excused” category is appropriate, but suggests that someone other than the researcher decide what is to be an excused protocol, although it need not be an IRB member. The reviewer should be someone knowledgeable about risks. Yale also proposes a brief waiting period before excused research is commenced.

d. For biospecimens, Yale proposes a middle ground between consent and no consent: a process of notification about the potential future use of remaining or leftover samples in research. Yale believes notification satisfies the ethical requirements of respect for persons. Moreover, a national campaign could be used to educate the general public on the importance of biospecimens to research and to the advancement of health care (Id. at 4).

There is significant alignment between the comments of AAMC and Yale on the issues discussed above. It would appear that the academic community, as represented by these entities, is in favor of many of the proposals in ANPRM, with some tweaks or small modifications. Both entities have discussed areas of concern beyond the 74 questions posed, and have determined areas that were not addressed by OHRP in the ANPRM. Both agree that more frequent guidance is needed from OHRP in clarifying the application of the Common Rule. Determination letters have become an inappropriate

substitute for guidance documents. In addition, OHRP should make an effort to more clearly define important terms. Significantly, AAMC suggests that the current definition of “research” with its focus on “generalizable knowledge” is not really helpful as every academic pursuit can be said to intend to contribute to generalizable knowledge. Researchers at Yale are apparently frustrated over the application of the regulation requiring certification that the funding application is entirely consistent with any corresponding protocols submitted to the IRB. It is Yale’s experience that the likelihood that the proposal for funding compares identically to the protocol is remote, so that the requirement is nearly impossible to meet and should be revisited.

2. IRB Affiliates

AAHRPP

The Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) is a nonprofit body that accredits human research protection programs including hospitals, IRBs, sponsors, universities and VA facilities within 234 organizations representing more than 1,100 entities that conduct or review research involving humans. (AAHRPP comments)

a. With respect to informed consent, AAHRPP proposes that documentation of consent should be permitted in ways other than signed written forms. There are instances where

other forms of consent, for example, oral consent for the illiterate, would better serve this population. Currently, when these individuals are enrolled, researchers may be noncompliant with the federal regulation. Further, AAHRPP does not support the use of templates, since IRBs already are too rigid in the development of consent documents under the current regulations. Guidance from OHRP would be much more helpful in allowing IRBs to feel secure in differing from the constraints enumerated in 45 CFR 46.116. IRBs should understand that they have flexibility to construct consent documents that are informational and comprehensible (AAHRPP comments, at 5-6). AAHRPP finds that the current requirements for consent form disclosures are paternalistic, including information that the researchers think participants would want to know rather than what may be more pertinent to what participants actually desire. In fact, some disclosures not only make no sense but also may be ethically inappropriate. An example of such a disclosure is including a statement that not enrolling or withdrawing would not result in the loss of any benefits when there are no benefits to lose (Id. at 14). Most importantly, the consent process should be seen as a process of education about the proposed research study and not just a form.

b. AAHRPP supports the concept of a single IRB for multi-site studies and hopes this revision will serve to harmonize the requirements of IRB review of such studies under the Common Rule with FDA regulations. AAHRPP also hopes that the revision would set a clearer expectation of the responsibilities of the local IRBs that currently review multi-site studies and believe they can change the protocol. AAHRPP believes that this is a

false expectation that leads to frustration and unnecessary burdens on the local IRBs. In essence, when it comes to multi-site studies, local IRBs are limited to deciding if the institution will participate in the study at all, and to providing slight modifications to the consent documents to meet local requirements (Id at 10). However, AAHRPP agrees with the commentators discussed above that, if a central IRB is mandated, OHRP must provide guidance to clarify the role and responsibilities of the local IRB. Another question raised by AAHRPP deals with whether the proposal deals with smaller multi-site studies, for example, community-based intervention studies involving only two to five local institutions. Indeed, the term “multi-site study” will need to be defined, as proposed by academia.

Guidance will also be needed on the role of a central IRB for continuing review, review of modifications, the addition of research sites, and other post-approval monitoring issues. Other potential considerations identified by AHRPP include the application of state specific laws, the identification and management of potential conflicts of interest, validating the experience and expertise of the research team, and funding a single IRB (Id. at 11). An important observation of this organization is that OHRP must be clear on whether it will hold the institution, the IRB, or the researcher responsible for specific regulatory requirements, and who is liable if a problem develops. It is suggested that OHRP will need to find an alternate mechanism, besides inter-institutional agreements, if a central IRB is mandated. AAHRPP disagrees with limiting central IRB review to domestic studies, opining that foreign sites may wish to use the single IRB model as well.

c. AAHRPP supports the risk-proportionate model for review and oversight of research (Id. at 11). As suggested by academia, minimal risk should be re-defined, and should refer to risks of harms and discomforts ordinarily encountered in the daily life of the “average person,” not the patient or any other specific population where the daily risk of harms and discomforts is higher (Id. at 12). AAHRPP also urges OHRP to consider permitting someone other than an IRB member to review certain types of research in order to reduce the burden on IRBs while still maintaining adequate protections for participants. However, the competence criteria for such reviewers must be described clearly and carefully. AAHRPP further favors the elimination of the expedited risk categories. Instead, all research involving minimal risk (as defined) should be eligible for expedited review (Id. at 11).

AAHRPP strongly disagrees with creating an “excused” category, citing that the new term will only serve to exacerbate the existing confusion. While AAHRPP agrees that the current practice of using exempt categories is burdensome and can be improved, it still suggests keeping these categories and permitting institutions and IRBs to make exempt determinations prior to the start of research. There is certainly no support for allowing researchers to make their own determinations. AAHRPP adds that anecdotal evidence from some accredited organizations suggests that between one-quarter and one-third of researchers misclassify research as exempt when it is not exempt. The exempt determination should be made by individuals knowledgeable about the regulations, who

know how to apply minimal appropriate protections and are not conflicted in making the determination. Such individuals could be, but need not always be, IRB members (Id. at 7). AAHRPP makes another noteworthy comment regarding how HHS expects to hold an institution responsible for the researcher's determination if the institution or its IRB has not taken part in the decision to exempt or excuse the research. While this may speed up the process, it seems more akin to having the fox guard the henhouse.

AAHRPP also takes issue with how the ANPRM appears to assume that the only risk in social and behavioral studies is an informational risk. While this may be accurate in some studies, other studies could include physical, social, or psychological risks. The Common Rule should give IRBs flexibility to deal with these risks, even in the context of minimal risk research. Furthermore, the audit requirement for excused research will merely add to the burdens of IRBs and researchers while not enhancing protections. Indeed, the ANPRM does not even address what happens when an auditor finds that a study was improperly classified as excused. What if the study is already complete?

d. It should not be surprising that AAHRPP was quiet on the use of biospecimens issue but did set forth other areas of consideration to OHRP more in line with AAHRPP's mission. For instance, AAHRPP points out that the ANPRM provides an excellent opportunity to add an education requirement for IRB members and researchers. In fact, AAHRPP opines that, if HHS proceeds with rulemaking that places more responsibilities

on IRB members and researchers, it will be essential to provide proper training. Along these lines, AAHRPP also urges HHS to add a section to the regulations on responsibilities of researchers, so that it is clear that protecting human subjects is a shared responsibility of both IRBs and researchers, and to reduce any confusion that might exist. Lastly, AAHRPP supports allowing IRBs to determine how frequently to review approved research, and rejects the notion that IRBs must report when they choose to override provisions for the use of expedited review and perform a more expansive review. AAHRPP affirms the HHS position that the regulations are a “floor” and not a “ceiling” (Id. at 15).

PRIM&R

PRIM&R is a non-profit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served a full array of individuals and organizations involved in biomedical, social science, behavioral and educational research via a wide variety of conferences and other educational activities (PRIM&R comments at 1)

a. PRIM&R objects to the ANPRM focus on the consent form and not the consent process that is central to the protection of human subjects. PRIM&R suggests that OHRP should focus on improving the process, with particular emphasis on the ongoing and iterative nature of the consent process, the responsibilities that investigators bear, and

the method for ensuring that robust informed consent actually takes place (Id. at 4). PRIM&R further opines that OHRP might consider explicitly suggesting the use of professionals with expertise in patient education as representatives of the investigators in the consent process, although the responsibility of obtaining informed consent ultimately lies with the investigators (Id.). Consent forms should memorialize what has happened in the consent process, and should not be the primary method of providing information on risks, potential benefits and alternatives to potential subjects. The consent forms currently in use have evolved into long, complicated, legalese documents designed to protect institutions, sponsors and investigators, and not to educate subjects (Id.). PRIM&R finds it surprising that, while virtually no one involved in human subject protections finds the current forms useful or appropriate, there seems to be widespread reluctance to changing them. PRIM&R believes it would be incorrect to blame IRBs for this problem as sponsors, institutional lawyers, risk managers, and others are primarily concerned with institutional protection rather than subject information (Id. at 5). Thus, PRIM&R suggests abandoning the terms “forms” or “documents” and, instead, referring to “educational materials for potential subjects.” This would immediately change everyone’s understanding of the materials from a legal purpose to an educational purpose. The materials should be written in a language subjects could understand and embody the concept that not all of the information need be included in one document. Furthermore, the boilerplate that most every institution uses for research permission should be provided in a separate document. A brief form should accompany the educational materials so that the potential subjects could affirm that they have read and discussed the educational materials and, having done so, agree to

participate (Id. at 7). Lastly, PRIM&R disagrees with a limit on the length of consent forms and believes that templates should only be guidance and not mandatory. It is interesting to note that PRIM&R believes that, if templates are created, the templates should be drafted by bona fide health educators and experts in health communications, and not by regulators, lawyers or others who regularly use language that is not understood by everyone (Id.).

b. PRIM&R supports centralized review of multi-site studies but is not in favor of the proposal to mandate that there be one IRB of record for all multi-site studies. Institutions should have flexibility in the protection of human subjects, and should never be required to justify additional review or the adoption of additional measures to protect subjects. It is PRIM&R's view that no institution should be excluded from participating in a multi-site study because it refuses to rely solely on an external IRB to review the protocol (Id. at 11). PRIM&R sees a distinction between central IRB review and centralized review. Institutions may voluntarily enter into some central review process but should never be relieved of their ultimate responsibility to protect human subjects within their institutions. For instance, institutions could participate in a central review in some sort of consortium model without ceding review responsibility to an external body. Each institution could also decide on a case-by-case basis whether or not to participate, depending on the nature of the research proposed or the institution's needs. Also of interest, PRIM&R suggests that, if a central review board is used, the term "IRB" is no longer appropriate and should not be used. IRB connotes "institutional" and a central

board is not part of the institution conducting the research. Rather the term “research review committee” or “research review board” should be used to better reflect the review process (Id.).

c. PRIM&R does not support the ANPRM proposal of an all-inclusive list of research activities that qualify for expedited review, nor for a federal panel to review the proposed list for periodic updates. Rather, PRIM&R prefers that the regulations set out criteria for what constitutes minimal risk, so that IRBs can apply these standards to specific research proposals and make the determination if expedited review is appropriate. Further, it would be helpful to IRBs for OHRP to create an illustrative list of the types of research that may be eligible for expedited review, together with reasons why these activities are placed on the list (Id. at 12). PRIM&R strongly believes that IRB review of any research designated as eligible for expedited review be subject to all the criteria in 45 CFR 46.111. Standards for approving research should not vary, as all subjects are entitled to the same substantive protections regardless of the method of review. Expedited review is only meant to be quicker (Id.). Expedited review should be done by an IRB staff person or board member to avoid confusion in the ANPRM about the use of some other “qualified” person. IRB staff and members are automatically qualified, assuming the means of education and preparation of IRB members and staff is adequate. PRIM&R also rejects the use of both the terms “exempt” and “excused” and proposes the single category, “research not subject to review.” Moreover, it is not researchers or investigators who should be authorized to make the determination of what qualifies as

“research not subject to review.” PRIM&R believes that some documentation of the study needs to be prospectively approved by an IRB staff member or board member before the protocol commences, and does not support registration and retrospective audits as adequate protection of human subjects (Id. at 13).

d. PRIM&R does not agree with the proposal that written consent be required for all biospecimen research. The status quo, whereby unidentified biospecimens may be used for research without consent, is appropriate, and does not violate the rights or welfare of subjects. In addition, requiring consent for all uses of de-identified biospecimens would make it prohibitively difficult to conduct research (Id. at 8).

It is clear from the PRIM&R comments that it believes it is the institution that has responsibility for protecting human subjects and that IRBs, as delegates of the institution, carry out that responsibility, but do not relieve the institution of ultimate responsibility. PRIM&R faults the ANPRM for focusing on the IRB as the protector and largely ignoring the institution or the researcher. Similarly, IRBs do not interact with subjects or write consent forms; these are the roles of the sponsor or the researcher. PRIM&R strongly urges OHRP to remind sponsors and researchers that they actually design and conduct the research and are, therefore, primarily responsible for human subject protections. PRIM&R sees this problem as arising from the Common Rule’s emphasis on institutions and IRBs as opposed to sponsors and researchers. If federal regulations

more closely applied to sponsors and researchers, then sanctions for violations could be more specifically imposed on the actual wrongdoers rather than on the institution as a whole. Applying sanctions directly to sponsors and researchers would more effectively encourage practices that enhance protections than does cutting off funding to entire institutions. Further, the current draconian practice wreaks havoc with research that other investigators are carrying out ethically and in compliance with the regulations (Id. at 3). Lastly, PRIM&R makes clear that, while the stated intent of the ANPRM is to make the process of human subject protection more efficient, efficiency itself is not a moral imperative or even an ethical value. Human subject protection should not be compromised by a desire for efficiency.

C. ANPRM: Summary of Comments by Edward E. Bartlett, Office of OHRP

As noted above, the Summary of Comments expresses the view solely of the author, Mr. Bartlett, and does not represent the official position of HHS or OHRP.

a. The regulations regarding informed consent forms would be revised under the ANPRM to provide greater specificity on content, length, readability, and possibly provide a template to be used by researchers in crafting the consent forms. Respondents strongly supported the ANPRM contemplated modifications to improve the quality of consent forms, with those opposing still favoring the general concept but expressing concern that

the proposals were overly rigid. A majority of respondents also supported the development of guidance designed to encourage the enhancement of reader comprehension (Summary comments, at 17).

b. The ANPRM suggests requiring central IRB review by a single IRB of record for all U.S. sites in a multi-site study. The comments report that this issue attracted a large number of responses, with respondents nearly evenly divided. Researchers and disease advocacy groups tended to favor the single IRB review requirement, while IRBs and institutional representatives tended to be opposed. Interestingly, the Pharmaceutical Manufacturers Association (generally subject to FDA regulations) strongly supported the concept of central IRB review, citing the burdensomeness of the present system of multi-site IRB review in terms of added expense, time delays and numerous revisions to informed consent documents without added human subject protections (Summary comments, at 15). Across the proverbial aisle, the University of California opines that reliance by multiple sites on a single IRB of record can raise complexities that are a rational, legitimate basis for opting out of any agreement to accept central review. Such complexities as adverse event reporting, conflicts of interest, and others need to be addressed by OHRP before central review is mandated (Id.). Respondents also recommended criteria for selecting the IRB of record: location of the principal investigator; one having expertise in the specific area of research; an accredited IRB and an IRB that is being monitored or audited by a federal agency (Id. at 16).

c. On the question of risk-based protections and the use of exempt and/or excused categories in the Common Rule, a strong majority of respondents favored clarifying the definition of research and broadening the exemptions. For the most part, it was categories relating to the social sciences that commenters identified as areas that could be removed from regulatory oversight (Summary comments, at 4). A strong majority also opposed the notion that researchers could assess exempt status, finding they generally lack the objectivity and expertise necessary. Commenters also favored at least a brief waiting period before research is begun, even if determined exempt or excused, but were opposed to an auditing requirement, favoring at least some level of IRB approval (Id. at 6).

d. A strong majority of commenters were opposed to the ANPRM suggestion that consent be required before research could be conducted on existing, de-identified biospecimens. (Summary comments, at 9) If the new proposals relating to biospecimens are adopted, the nearly unanimous view favored the grandfathering of previously existing biospecimens with the rule applying prospectively only (Id. at 11).

D. If the ANPRM Revisions Were Law

In Chapter 2, examples of recent research abuses at highly reputable research institutions were discussed. These unfortunate mishaps occurred despite IRB review. The next

inquiry is whether and to what extent the outcomes of these cases would be different if the revisions proposed in the ANPRM were the governing regulations.

a. In the case of Jesse Gelsinger, the outcome could very probably have been different if the current proposals regarding informed consent were adopted, at least as modified by the commentators. The consent forms signed by Jesse Gelsinger and his father were shown to have left out critical information regarding the risks attendant to the research protocol. Although the Gelsinger lawsuit was settled out of court so that no real findings of fact were made, it is documented that information relating to the death of monkeys in previous studies of this intervention was not revealed in the consent documents, as well as other adverse events that should have been reported to the FDA, but were not. Possibly, if the regulations were harmonized so that there could be no confusion regarding what is required by the Common Rule and what is required by the FDA, more fulsome disclosures could be made. One must also consider whether having a simple one or two page actual consent form, but a detailed appendix with a patient or subject educator to explain the risks, may have prevented Jesse's death. Jesse may have had a better understanding of the risks and may not have enrolled in the study at all or he may have been more keenly aware that his ammonia levels did not warrant participation at that particular time. Another area of concern regarding the trial in which Gelsinger participated is that the researchers and the institution had substantial financial interests in the outcome of the trial. It should be noted that the ANPRM is silent on researcher conflicts of interest. This presents an opportunity for future consideration.

b. *Grimes v. KKI* is another example of how the consent process could have been enhanced to provide better information regarding the very real risks, to foster better understanding through a neutral subject educator, and to provide support to subjects and their families through community involvement. It should also be noted that the participants in the study were solicited by approaching landlords of low-income housing instead of approaching the tenants directly. Surely, landlords had self-interest in filling their substandard residences. Participants were enticed with small amounts of money and gifts. Here, there was significant evidence developed that the consent form did not adequately inform, and that it was not well drafted or comprehensible. This lead paint study was ultimately found to have no therapeutic value to the healthy minor subjects and, as such, should not have been undertaken. It has been suggested that the IRB misconstrued the real risk of the study, which was lead paint exposure, not the blood draws.

c. The Roche case is yet another example of not only an incomplete consent process but also a problem with the entire IRB supervision of the research protocol. The IRB was faulted for not having an entire board discussion of the protocol. Individual members reviewed a protocol and reported to the board. If the board had no questions, the protocol was presented for a vote, generally obtaining approval. The ANPRM may help in this type of situation if the IRBs are freed of some administrative burdens so that more resources can be devoted to the riskier studies. This case cries out for better IRB,

researcher, sponsor and institution training and education in the federal regulations, the risks of research and the need for protections. Unfortunately, the ANPRM does not directly address these needs.

E. Last Thoughts on Changing the Federal Regulations

This thesis has tacitly adopted a basic presumption: that HHS has the authority necessary to amend the Common Rule. A federal agency derives its informal rulemaking authority from the Administrative Procedures Act (APA). Informal rulemaking has been an important way for agencies to promulgate and amend regulations (Evans 2012). Under the APA, a federal agency develops a proposed regulation (NPRM), publishes notice of the proposed rulemaking in the Federal Register, and allows a period for the public to submit written comments. Thereafter, the agency may withdraw its proposal, revise it, or promulgate a final regulation. The process is deemed “informal” since no formal evidentiary hearing is required (Evans 2012, at 2).

HHS did not follow this procedure in its July 2011 publication of the ANPRM. In this case, HHS asked for comments on 74 questions relating to possible reforms of the Common Rule in an “advance notice” rather than in a “notice.” Additionally, no specific regulatory text was proposed for consideration, as would be provided in the “notice” step. An ANPRM is merely an inquiry of the public, which sets forth areas where the agency may consider regulatory action. The APA requires the NPRM but not

the ANPRM. So why go the ANPRM route if it is not required? Certainly, the ANPRM has drawn comments from interested stakeholders and has provided input for HHS' consideration prior to it taking the next step and publishing an NPRM. Not surprisingly, interested stakeholders possess significantly divergent views on most areas of potential rule revisions. This raises the question of whose views are deserving of greater weight or consideration in promulgating rulemaking. Whether there are statutes for guidance or whether the agency may need to seek additional authority from Congress are beyond the scope of this paper despite the fact that these interesting questions could underlie the delay in HHS publishing an NPRM for the Common Rule.

Notwithstanding the authority inquiry, it remains to be seen whether all, or for that matter any, of the contemplated reforms proposed in the ANPRM could be accomplished, particularly given the varied constituencies affected, and their potential influence. It would seem, for instance, that harmonizing the federal regulations and streamlining multi-site study reviews would benefit the pharmaceutical industry, which has some political clout, especially in creating jobs in a struggling economy. Others may find fault with the single IRB review process and want to maintain individual IRBs, or at least shadow IRBs, if liability will remain with the institution conducting the actual study.

Some commenters cite the varied interests of the agencies that have subjected themselves to the Common Rule as evidence that the ANPRM is stalled and not likely to

move forward, at least not anytime soon. There may be some basis for this conclusion as demonstrated by the delays experienced so far. This leads to a further consideration of whether it is really regulatory reform that is needed, or whether similar results could be accomplished more efficiently by enhanced OHRP guidance for certain of the proposed changes. An example is the concept of centralized IRB review. The regulations, as currently written, do not prohibit this practice, but uncertainties about ultimate responsibility for the research approvals, etc. cause institutions to shy away from this process. OHRP guidance relating to the areas of concern could facilitate the use of a central IRB for a multi-site study much quicker than the current ANPRM proposal. Surely, some involved stakeholders believe that the Common Rule is hopelessly out of date and that modernization is desperately needed. As has been noted above, there is a consensus that IRBs are stretched beyond their limits, that they are poorly resourced, that they are too dependent on the dedication of volunteer members and that, essentially, they are expected to do too much with too little. There can be no doubt that IRBs need to devote their time and talent to activities that truly protect the subjects of research. However, can these goals be accomplished more simply and effectively through regulatory guidance than through regulatory reform? While it is hard to take exception to the general comments that the IRB system is failing and flawed in some areas, it should be recognized that it has worked, at least fairly effectively, for many decades. Should the OHRP be directed to establish practical guidance for implementing the current regulations in a way that promotes clarity and enhances understanding, the current regulations may still be the best available protection for human subjects.

Since Nuremburg, the cornerstone of ethical research has been voluntary, informed consent. The current regulations provide safeguards for this right. Certain of the proposed reforms dealing with enhancing the informed consent process are important and valuable adaptations of the rule. However, doesn't the rule already allow such adaptations and couldn't these goals be accomplished with specific guidance, perhaps with a notice and comment period? Page limits on the consent form and designated language would do little to promote understanding. As several commenters to the ANPRM have already noted, it is the process, not only the documents or the forms, that is in need of attention. Some are critical that IRBs tend to see review of consent documents as a task that mainly involves editing the text of forms and not focusing on an adequate risk assessment or ensuring that potential subjects are properly guided through the process. OHRP guidance on the process, with possibly the addition of a neutral educator or "consent navigator," could go a long way towards accomplishing the goals stated in the ANPRM.

Developing consensus among all, or substantially all, stakeholders to reform the current regulatory scheme can be an overwhelming task. Developing guidance within the current regulatory framework could solve some issues identified as challenges to human subject protection. Any real or perceived deficiencies in the Common Rule will not be entirely eliminated by the ANPRM. Could it be that some of the problems ascribed to the implementation of the Rule are more appropriately ascribed to the research institution's perception of the Rule? Is the Common Rule just a burden to be complied

with, or circumvented, as needed to promote the furtherance of research? One must really ask whether the current efforts at reform really arise more from frustration with, or resentment at, being regulated. It has been argued that some of the proposals in the ANPRM could be considered safe harbors for researchers. Is this truly enhancing protections? These are, for the most part, unanswerable questions that can only be viewed from hindsight, if and when the ANPRM revisions are implemented.

CHAPTER 4

A. Vulnerable Research Subjects

In terms of biomedical or behavioral research involving human subjects, vulnerability has typically been understood as the inability to give or withhold informed consent and the likelihood of being misled, mistreated or otherwise taken advantage of (Iltis 2009). The Belmont Report focuses on a compromised capacity for consent as a foundation of vulnerability, while the Council for International Organizations of Medical Sciences (CIOMS) broadens the definition of vulnerable persons to include “those who are relatively (or absolutely) incapable of protecting their own interests” (Id. at 7). The Common Rule provides specific protections for certain vulnerable categories: prisoners, children, pregnant women and fetuses. A category of potentially vulnerable research subjects that has been overlooked in terms of any specific federal regulation is the population of adults with impaired decision-making capacity. This is not the result of lack of attention or effort but rather a failure of consensus. Since the 1970s, several attempts have been made to draft regulations for decisionally impaired adults, only to have these efforts fail for lack of agreement during the comment period. Interested stakeholders frequently disagree on two important questions with respect to the decisionally-impaired: how research involving this population should be regulated, and who, if anyone, should be permitted to consent to research on behalf of adults who have limited or no decision-making capacity (Tovino 2013). This lack of specificity for subjects with impaired mental capacity has led to both a chilling effect for some researchers and a lack of adequate oversight for others.

Carl Coleman notes that the Common Rule uses the word “vulnerable” three times (Coleman 2009). First, 45 CFR 46.107(a) provides that IRBs that regularly review research involving a vulnerable category of subjects should consider including one or more individuals experienced in working with these subjects. Second, 45 CFR 46.111(a) (4), dealing with the equitable selection of subjects, directs IRBs to be particularly aware of special problems of research involving vulnerable populations. Lastly, 45 CFR 46.111(b) requires “additional safeguards” when some or all of the subjects are likely to be vulnerable to coercion or undue influence. Nowhere does it state what those additional safeguards should be although some of the ambiguity is resolved in subsequent subparts dealing with the specifically regulated populations of children, prisoners and pregnant women (Id. at 13). The Common Rule does not define vulnerability but does provide examples: children, prisoners, pregnant women or handicapped or mentally disabled persons as well as economically or educationally disadvantaged persons (Id. at 12). These disparate groups may be vulnerable in one situation but not in another. Children or mentally disabled may be unable to give truly voluntary informed consent while prisoners may be subject to undue influence. Thus, vulnerability is not a stand-alone concept but a relational one. Few people are simply vulnerable: they are vulnerable to something (Id. at 14). As Coleman further notes, even though there is no consensus on what vulnerability actually means, there is an intuitive ethical appeal to calls for protecting the vulnerable (Id.).

B. Decisionally-Challenged Adults

The gap in regulatory guidance for research on decisionally-challenged subjects should be addressed. The ANPRM does not directly address the lack of specific regulations. Certain of the 74 questions in the ANPRM dealing with consent provided an opportunity for commenters to voice concerns regarding research participants with decisional or cognitive impairment. The specific questions deal with the adequacy of consent forms, the level of research participant comprehension required, and the desirability of additional consent process requirements (Tovino 2013, at 791). This is still a long way from specific regulation or even specific guidance. Scientific investigation of cognitive disorders is one of the most ethically challenging areas of clinical research. It pits society's interest in acquiring knowledge and advancing the general good against the interests of individuals who lack the capacity to make personal decisions. Such individuals often suffer social stigma long associated with mental illness, causing either an exaggeration of deficits or an under-appreciation of strengths (Tovino 2013, at 797).

Several states have guidance on medical or treatment decisions for decisionally incapacitated adults; however, most do not have guidance on research for this group. Even when state specific guidelines do exist, they are more like a patchwork of disparate rules than a clear, consistent road map for researchers and IRBs. Federal and state governments have swung back and forth between the competing goals of protecting vulnerable human subjects while fostering biomedical and behavioral health research (Id.). Some states support such research with few restrictions, and other states prohibit

all such research without the prospect of either direct medical benefit to the subject or obtaining generalizable knowledge about the subject's specific disorder or condition (Id.).

On the federal level, over the past three decades, various commissions and regulatory agencies have provided recommendations on issues relating to research with the decisionally impaired. The National Commission issued a report on February 2, 1978 relating to human subjects research involving institutionalized individuals with "mental infirmity" (Tovino 2013, at 798). The Commission recommended that individuals who lack decision-making capacity be allowed to participate in minimal risk research, but only if the research is related to the individual's condition or the individual assents or does not object to the research (Id.). For research that posed greater than minimal risk, the Commission recommended that the research hold out the prospect of direct benefit to the individual (Tovino 2013, at 799). Although DHEW proposed regulations later in 1978 based on the Commission's recommendations, such proposed regulations were never enacted. The proposed regulations would have allowed minimal risk research to proceed so long as it was relevant to the participant's condition, the individual assented or did not object and the individual's legally authorized representative consented. The proposed regulations would have further allowed the conduct of greater than minimal risk research using decisionally-challenged adults if the research involved an intervention that held out the possibility of direct benefit to the participant and the risks were justified in relation to the anticipated benefit, the individual assented to participation and the individual's legally authorized representative consented to the individual's participation.

Lastly, the proposed regulation would have allowed greater than minimal risk research even if the research did not hold out the prospect for direct benefit if the risk involved only a minor increase over minimal risk, the anticipated knowledge was of vital importance for understanding the individual's condition, and the individual gave informed consent to participation. If the individual lacked capacity to give informed consent, the Commission would require the individual to assent to research participation and the individual's legally authorized representative (LAR) to consent to the individual's participation. If the individual lacked the capacity to assent but did not object, both the LAR and a court must consent to the individual's participation (Tovino 2013, at 799, 800).

Furthermore, in its 1978 report regarding research with the mentally infirm, the Commission found it advisable to make use of a disinterested third party to ensure that the research is not harmful. This individual might also play the role of a consent auditor, one who monitors the informed consent process itself and determines whether the potential subject has given a truly competent consent. (Moreno 1998) Moreno further reports that there is remarkably little literature on the process that led to the rejection of the Commission's recommendations on those institutionalized as mentally infirm in the early 1980s. (Id.at 13) Reportedly, one former Commission member, Al Jonsen, noted that both the National Institute of Mental Health and the Agency for Drug Addiction and Mental Health Administration objected that the recommendations would stifle important

research with their populations. (Id.) A consultant to the Commission, Harvard professor Neil Chayet, argued that the perspectives of law and medicine on informed consent are “fundamentally incompatible, particularly in the area of the mentally disabled, where appreciation of the concept of informed consent is well on its way to paralyzing research and treatment” (Moreno 1998, at 13 quoting Chayet 1976).

At the same time DHEW proposed these regulations, it also proposed regulations governing children. Those affecting children were adopted by DHHS in June 1983 but those affecting those persons with mental infirmities were not. In addressing why the latter were not adopted, the Secretary of DHHS pointed to a lack of consensus on the proposed regulatory provisions and a judgment that the general regulations governing human subjects’ participation sufficiently incorporated the National Commission’s recommendations (Proposed Regulations, 43 *Fed. Reg.* 53,950, 1978). The regulations do authorize IRBs to institute additional safeguards for research involving vulnerable groups, including the mentally disabled (Moreno 1998, at 14). The safeguards could involve consultation with specialists concerning the risks and benefits for these populations, or special monitoring of consent processes to ensure voluntariness. However, it is unknown how frequently IRBs actually implement these conditions (Id.). In fact, Moreno reports that there is strong evidence that IRBs are unlikely to compensate for the lack of specific regulations for research with the cognitively impaired by aggressive use of their discretionary authority (Id.).

State laws on this topic vary widely; to the extent they exist at all. In the 1990s, two states, Maryland and New York, established working groups to consider what legislation may be proposed to protect research involving persons with disorders that may affect decision-making capacity. Both of these groups' proposals contained many similarities. For example, both groups said decisionally incapable persons should not be enrolled in studies that could be conducted on persons able to consent (Dresser 2001). Likewise, both groups recommended that investigators should develop procedures for evaluating the decisional capacity of prospective participants and both said that capable adults should be able to make decisions about future research should they become decisionally incapable (Id.at 667). Both groups further found that in certain circumstances, it could be appropriate for relatives or friends to make research participation choices for those incapable decisionally, but that no research should be imposed on those who resist (Id.). Although the results of these working groups have provided guidance to researchers and IRBs, none of the recommendations resulted in state legislation or policymaking in this area (Id.at 690).

To date, the best guidance researchers and IRBs have regarding research involving individuals with impaired decisional capacity are non-binding recommendations. Examples of such guidance include the recommendations contained in a 1998 report issued by the Clinton Administration's National Bioethics Advisory Commission (NBAC), the November 2008 OHRP answers to frequently asked questions on this topic posted on its website, and the Subcommittee for the Inclusion of Individuals with

Impaired Decision-Making in Research (SIIDR) recommendations approved by OHRP in 2009 (Tovino 2013, at 804, 805). It should also be noted that on September 5, 2007, HHS published a formal request in the Federal Register at 72 *Fed. Reg.* 50966, seeking comments on whether additional guidance or a new subpart of the Common Rule is needed to address research involving adults with impaired decision-making capacity. Although the closing date for receipt of comments has come and gone, HHS has not issue any proposed regulation subsequent to its request for comments (*Id.*). However, in November 2009, the National Institutes of Health (NIH) released certain “Points to Consider” with respect to research involving individuals with impaired decision-making capacity. NIH particularly noted that many states do not have specific consent-to-research laws for this population, and stakeholders frequently rely on laws governing consent-to-treatment. It is telling that NIH concludes that IRBs may wish to consult legal counsel on issues relating to who can give consent for subjects of proposed research in this arena (Tovino 2013, at 806). These non-binding guidance statements provide flexibility for the researcher and IRBs in making research decisions, but may lead to either under or over-protection of the research subjects due to the lack of binding authority and significant researcher and IRB discretion.

All of this seems to cry out for federal regulation or at least specific guidance, which, unfortunately, as history reveals, is unlikely. It is certainly presumptuous to attempt to draft a regulation or a guidance document when those expert in the field have failed. It would seem that true reform, either as envisioned in the ANPRM or for a new regulation

offering enhanced protections for those with decisional impairment, would only become a reality in a perfect world where consensus could be found. It has also become painfully clear that such a “perfect world” does not exist.

C. Proposal

The first and least likely option would be to change the regulations governing research with the decisionally impaired. This option would offer the most effective means of guiding researchers and IRBs while, at the same time, protecting the interests of those unable to protect themselves. HHS could add new provisions to the Common Rule that would specifically govern human subject research involving adults with impaired decision-making capacity. This new provision could be codified at 45 CFR 46 (Subpart E). It could follow the basic policy in the Common Rule, Subpart A, and the special regulatory subparts dealing with the previously designated vulnerable categories of pregnant women, fetuses and neonates (Subpart B), prisoners (Subpart C), and children (Subpart D). This proposal will not attempt to draft the text of a new Subpart E. Alternatively, a second, somewhat less aggressive proposal would entail an OHRP guidance document on the expansion of duties of IRBs when dealing with decisionally impaired adults, rather than a regulatory change. Lastly, and most probably the best option given the current research climate, is enhanced efforts to educate researchers and IRBs alike.

1. Ethics Advisory Boards

In his seminal work, *The Birth of Bioethics*, Al Jonsen recounts how the National Commission, in several of its reports, suggested that certain kinds of research, particularly dealing with children, be submitted to a “National Ethics Advisory Board” that would be permanently established within DHEW (Jonsen 1998, at 106). Then Secretary Califano chartered the Ethics Advisory Board (EAB) in 1977. Its charter specified that the EAB was to be available for consultation on all DHEW programs and policies and it was to review all of the research protocols as envisioned by the Commission (Id.). As history reveals, less than 3 years after its inception, the EAB was disbanded due to lack of funding. Jonsen opines that the EAB “still hovers as a ghostly presence in the federal regulations, charged with mandatory review of certain types of research, but it exists nowhere in reality” (Id. at 107).

A legacy of the EAB may be Section 407 of Subpart D of the federal regulations governing children as research subjects. In pertinent part, Section 407 provides that research involving children that does not otherwise meet the requirements of the regulations may be allowed if a panel of experts is consulted and agrees either that the research does meet directives in the regulations or that certain further enumerated conditions apply. The proposed research must: (1) present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (2) be conducted in accordance with sound ethical principles; and (3) ensure that adequate provisions are made for soliciting the assent of

children and the permission of their parents or guardians (45 CFR 46.407(b)). One important distinction between the EAB as envisioned by the Commission and Section 407 is that the regulation nowhere provides that the “panel of experts” is a standing committee. Rather, it seems that it is convened ad hoc. Should such a panel of experts as already established under Section 407, be expanded to include experts dealing with the challenges of research involving decisionally incapable adults, it could significantly aid IRBs in effectively dealing with research protocols for this subject population. Possibly funding could be found to revive the EAB concept and allow the panel of experts to be permanently established to deal with research issues for both children and those with decisional impairment. IRBs would then be directed to seek the advice of such a panel on protocols with either of these subjects. This would help level the playing field among IRBs having varying degrees of expertise in dealing with issues particular to research with either children or with the decisionally impaired.

2. Guidance Adduced From Subpart D:

Subpart D regulations are based on recommendations developed by the National Commission that was established in 1974. It has been reported that research with children was one of the subjects to which the Commission paid particular attention (Wenner 2004). The Commission’s focus was on two questions: (1) under what conditions is the participation of children in research ethically acceptable, and (2) under what conditions may such participation be authorized by the subjects and their parents? (Id. at 259). The resulting regulations were not as clear as one might hope.

Ambiguities in interpretation exist, fostered in large part by the lack of definitional precision. A critical term lacking either a definition or an example is “minor increase over minimal risk” (Id.at 260). The lack of definitions results in widespread differences in how and what research IRBs approve. It is also possible that the lack of clear definitions, particularly in the area of risk, have allowed a gradual erosion of the protections intended by the regulations (Id.at 261).

Another area where the regulations may be eroded appears in the situation where the interests of the child may be in conflict with the interests of the parent, and yet the parent has the right to consent. An example of this exact situation can be found in the *Grimes v. Kennedy Krieger Institute* case discussed in Chapter 2 above. In *Grimes*, the court found that parents were enticed by financial incentives, food stamps, trinkets and other tokens to enroll their children (Id.at 262). Surely, parents, guardians or those entrusted with enrolling children in research may be motivated by other than the child’s best interests. Sometimes parental consent, no matter how informed, is insufficient. As noted above, the Maryland Court in *Grimes*, in a scathing opinion, lashed out at the current system of regulatory oversight for research with children. The court felt that the system was flawed, with IRBs lacking in objectivity and more concerned with the success of the research than with the ethics of it (Id.at 250).

The Children's Health Act of 2000 was enacted to address the disparity between the Common Rule (Subpart A) and Subpart D. The Act mandated that the federal protections under Subpart D apply to all federal agencies and also directed a review of the regulations by HHS. OHRP, pursuant to this directive, consulted experts in relevant fields and conducted a review of Subpart D (Id.). The resulting report concluded that the current regulations were sound and effective and well-crafted when IRBs properly implement them (Id.). The report, however, went on to suggest several definitional enhancements, or at least for HHS to provide additional guidance on certain terms and concepts, such as the proper procedures for recruiting subjects and providing parents with payments (Id.). Thus, it is clear that a panel of experts recognized ambiguities in the regulations that adversely reduced their effectiveness in providing the intended protections.

It would seem obvious that these same concerns can be addressed in the proposed new Subpart E, or in the proposed enhanced OHRP guidance documents, by more clearly defining terms and by more precisely guiding IRBs in the protocol reviews. This is easier said than done. The methods for imposing regulations or guidance on research, whether with children or with the decisionally impaired, are necessarily a result of compromise. How much protection is needed and how much progress will be impeded? This requires a weighing and balancing of interests with unavoidable conflicts among stakeholders. Examples cited earlier in this paper suggest that regulatory oversight on research with children is probably not as robust as it should be. Just using these

examples, Grimes, Gelsinger and Roche, would seem to support the notion that the federal oversight system of protections is flawed. This does not mean fatally flawed. What seems to come through loud and clear through all of this rhetoric is a widespread failure to understand the moral underpinnings of the federal regulations. Rather than promulgating more rules so that creative minds could find new and better workarounds, it behooves the OHRP to educate.

CHAPTER 5

A. Summing Up

The ANPRM addresses the dichotomy of enhancing or increasing the effectiveness of protections for human subjects in research while at the same time streamlining the process to increase efficiency and reduce burdens. This is a tall order. The ANPRM takes on the task of attempting to balance these two seemingly contradictory goals by seeking to revise and modernize the Common Rule. Many of the suggested revisions, either directly or indirectly, affect the use and functioning of IRBs. The proposals in the ANPRM indicate that HHS appears to be both increasing and, at the same time, decreasing the role of IRBs. IRBs are autonomous bodies set up by research institutions (or by private independent organizations) and staffed by these institutions, basically as a form of self-regulation. IRBs are charged with ensuring that adequate protections are in place in virtually every research study involving human subjects. An IRB provides both approval and ongoing oversight of all human subject research, other than those studies determined to be exempt. Therefore, it is easy to see that a research institution places a good deal of trust and responsibility in its IRBs. In fact, it has been noted that: “Trust in the honest, conscientious judgment of human beings who serve on IRBs is pivotal to the entire system of protection of research subjects. Indeed, the system recognizes that there is no simple formula to apply ethical decisions, and instead it vests the major responsibility of ethical decision making with the IRB” (Shelton 1999 at 6). It is, however, well documented that since the creation of the IRB model of oversight, research has changed dramatically. The increased number and complexity of studies, as well as the emphasis on such things as genetic research on tissue samples, has

caused IRBs to expand their scope and to shift their focus. As noted previously, this added burden on IRBs has resulted in chronic complaints of delay, frustrating researchers, sponsors and institutions.

With all this in mind, it appears that the ANPRM tries to relieve the increased burden on IRBs by pushing responsibilities for oversight both up and down. To explain, certain current IRB responsibilities, for instance, determining which studies are to be designated “exempt,” are proposed to become the responsibility of the investigator. Thus, it is presumably the proponent of the research study who is left to determine if a specific study is “excused,” with only registration and no IRB review. Other IRB responsibilities, for instance, those relating to review of consent forms, are probably being pushed up to the federal level under the ANPRM. With the use of specific page limitations and templates, the regulations rather than the IRB will dictate consent form requirements. Other examples of proposed federal rather than IRB oversight are the establishment of standardized data protections for minimal risk research and a list of exempt or excused research protocols that do not automatically go to IRBs.

As noted in the comments from academia and those concerned with IRBs above, there is substantial debate and uncertainty among constituencies as to whether investigators are adequately equipped to make the determination that their research studies do not need IRB review. The Common Rule, not unlike our U.S. Constitution, works on a system

of checks and balances. Placing too much decision making power into one branch or one entity encourages risk and warrants extreme caution. While there are laudatory goals in decreasing IRB oversight for certain studies, (those posing only minimal, informational risks come to mind), the idea of reducing the IRB's role in all minimal risk studies is, I believe, a potential minefield. Requiring only a one-page registration before a researcher could begin a study hardly seems appropriate protection in all minimal risk studies. It may be enough in certain interview or other informational risk studies, especially if the standardized data protections as proposed are adopted. However, this should not be applied universally, even to the proposed expanded list of exempt categories of research. It is also a mistake not to require at least a waiting period, or some form of IRB prospective review, before research begins. Random retrospective audits further burden IRBs for review of what may well be exempt research. In addition, a one-page registration form may not provide sufficient information to allow a retrospective audit to be effective. Another question raised by this proposal is what an IRB is to do if it determines that the original exempt status was misapplied. The ANPRM does not appear to answer this concern. While IRBs have been criticized for overestimating the degree of risk in certain studies that researchers believe should be exempt or excused, it is very likely that researchers themselves may underestimate the risk in their studies. Moreover, there is certainly no assurance that the regulations will be applied consistently by individual researchers reviewing their own individual studies. It is far more likely that IRBs will provide consistency in review, despite the fact that the alleged inconsistent application of the regulations is yet another criticism of IRBs. One last comment in this area concerns the ANPRM's silence on any training or educating of

researchers before they are allowed the responsibility of assessing their research protocols under the regulations for exempt categorization. Nothing is mentioned; therefore, it is assumed no training is anticipated. This is a mistake.

In addition, I would not agree that IRBs need to provide explicit justification before choosing to require continuing review of an expedited study. IRBs should be allowed the flexibility to determine when the protocol, originally given expedited review, should have further intervention. Removing the burden of stated intervals of continuing review is reasonable and should be included in the revisions. IRBs should be allowed to state when, at what intervals, continuing review, if any, should proceed. This can be handled on a case-by-case basis without relying totally on the investigator to prompt a further review. Notwithstanding, I agree, in principle, with the concept, proposed in the ANPRM, to align IRB review with the degree of risk. I do think this area needs more careful consideration of the proposed shift in roles and responsibilities.

The proposal of a centralized IRB for multi-site domestic studies has drawn a significant number of comments from stakeholders. In essence, there seems to be general agreement that centralized review is likely to increase efficiencies but must proceed with caution, which militates against immediate mandate. Many questions remain unanswered and may need to be addressed as this proposal is more slowly implemented. For instance, how does one avoid the race to the bottom in forum shopping for the most

lenient IRB? How will the selection process actually proceed? How will this central IRB be funded? Importantly, how is a shadow IRB at each institution involved in the multi-site study avoided, particularly if each institution continues to be held responsible for protecting the human subjects? How will site-specific, local concerns be addressed with a mandated single IRB review? Does a centralized IRB, while allegedly increasing efficiencies, actually degrade the role of IRBs on the institutional level? I do not think a mandated single IRB would necessarily degrade a local IRB, but precautions must be taken in the implementation to ensure that this does not happen. As noted in the comments above, efficiency is not an ethical value or a moral imperative, while safeguarding research subjects certainly is. A good place to start with centralized review may be those IRBs already developed by particular groups or consortiums, such as the National Cancer Institute. By use of these IRBs, with experience in a sort of central review, and a measured, careful implementation of the proposed revisions in this area, unintended consequences can be minimized and human subject protections maintained.

As currently constructed, no consent is needed for research on currently existing biospecimens. Most commentators appear to agree that the status quo offers the appropriate level of protections to the subjects so long as the specimens do not identify the individual from whom they were obtained. This allows research to proceed without the encumbrance of searching for the tissue donors and obtaining consent, sometimes long after the tissue samples were gathered. I would agree that it is unnecessary to

require researchers to obtain consent under these circumstances since no violation of an individual's autonomy or right of self-determination can be found if there is no identifiable relationship between the donor and the sample. The ANPRM proposal of consent for future use of anonymized biospecimens adds another layer of administrative burden for probably no additional protections. Concerns here appear to arise from a notion that in the not too distant future, there will be no such thing as unidentified specimens. DNA will allow the source to be identified so that consent upfront is the only way to ensure that research efforts can continue. As for identified or identifiable specimens, the present regulation offers more protection than a general consent to future use, since currently specific consent is obtained at the time of donation with specific future uses set forth, not just open-ended "future use." One other anomaly in the ANPRM is the question of how "informed" consent can be for unspecified future research at some unknown time, place, etc. Does this really qualify as additional protections for anonymous donors of tissue samples for research? How informed can consent be?

Before jumping in with both feet to repair what may not be broken, perhaps OHRP should step back and reassess the best way to accomplish the goals of the ANPRM. I would posit that not all stated goals need to be accomplished through regulatory revisions. Certain proposed revisions could be the subject of OHRP guidance with appropriate efforts to educate the constituents. This proposal is particularly applicable to proposed changes to those areas of IRB oversight that are actually already encompassed in the current regulations. IRBs are charged with applying the ethical principles underlying the federal regulations to research efforts. The ANPRM is apparently

attempting to raise decision making to the highest level possible in an effort to eliminate or reduce confusion or inefficiencies across agencies and institutions following the Common Rule. This proposed effort to increase efficiency comes at the cost of reducing the flexibility currently afforded individual IRBs. Providing federal uniformity may allow IRBs to better focus on risk levels of research protocols, but at what cost? Will IRBs lose the flexibility to apply ethical values to research proposals as they see fit?

Certainly various agencies that have adopted the Common Rule view research efforts from their own unique perspective. They may oversee different types of research or different phases of research as it is conducted. Again, while uniformity is a laudable goal, each agency should retain the ability to issue guidance on how the regulations affect research from their unique perspective. The proposal in the ANPRM regarding achieving consensus across regulatory agencies may actually undermine the efficiencies sought. The idea that agencies reach consensus before guidance could be issued is probably a show stopper. As noted by Shelton, the flexibility IRBs enjoy to tailor protections to specific research situations should be seen as a virtue and not a vice (Shelton 1999, at 6).

Acknowledging that the ANPRM is only an “advance” notice and not the actual notice and that it does not incorporate any proposed new regulatory language, it also does not provide any overt connection between the changes and any ethical principles. Moreover,

it does not specify how IRBs should proceed with novel cases to be decided under the new regime (Id. at 9). A high-level review of the seven categories of regulatory reforms in the ANPRM shows that many of the categories overlap. Thus, it is challenging to separate specific proposals as worthwhile and others as redundant, or already allowed in the current regulatory scheme. Careful consideration should be given to those areas of flexibility already allowed in the rules, but which either IRBs or researchers are afraid to implement for fear of regulatory reprisals. One such area is the proposed mandate for centralized IRB review of multi-site studies. There is no need for such a mandate. First of all, the idea is fraught with potential problems. Serious guidance and adequate consideration is needed before such a mandate makes sense, if it ever does. Next, the current rules allow for centralized review so, again, a mandate is unnecessary. If OHRP guidance and education efforts were enhanced, there would be no need to even consider such a revision. Trusting IRBs to do the right thing is foundational in both the ethics and the legal regulations of human subject research. Given appropriate guidance and education, one can only hope that the trust is well-placed. IRBs have been described as over-burdened, stressed and, at times, inefficient. Adding a dimension of education would seem, at first blush, to only exacerbate these concerns. However, a short education session at some point in every, or possibly in every other, IRB meeting could alleviate some of the stresses by having a higher functioning team, more sure of and in tune with its ethical mandates. Enhanced educational efforts combined with certification, and possibly audits conducted by certifying entities, may be all that is needed to allow IRBs the flexibility that the drafters of the current regulations envisioned.

Without detailing several of the other suggested provisions of the ANPRM, I would just like to add a few comments here. First, harmonization of various regulations relating to human subject research is a worthwhile effort that could be very helpful to researchers, IRBs, sponsors and institutions in knowing what they are dealing with. However, as noted above, it must still allow the flexibility that already exists for agencies to tailor guidance as needed. Progress in streamlining and promoting efficiencies should not be at the cost of protections. These considerations must be kept in mind as regulatory reform moves forward. Second, I would support curtailing IRB review of certain social science or behavioral studies where the risks are not physical or psychological but solely informational. Third, the tailoring of IRB oversight to the degree of risk should be seen as a virtue and promoted in any reforms to the regulations. There can be little disagreement with the concept of utilizing IRB resources on the studies that have higher potential for harm. Coordinating procedures and processes across institutions to more efficiently manage the complexities of multi-site studies can afford IRBs relief from duplicative review. It should be noted that it is not uniformity and efficiency that are, or should be, the goals in and of themselves. They are not the moral imperatives that underlie the federal regulations. When these goals are combined with a system that offers IRBs the flexibility to tailor specific protections to individual research protocols, progress will be made towards an enduring system of human subject protections.

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