Ethical Considerations in Research on Human Subjects

A Time for Change… Again[1]

Research using human subjects will continue to play an important role as part of a great humanitarian effort to understand ourselves better and to relieve distress and disease.

To use human beings as subjects in medical experiments – or any type of research – is a special privilege which carries with it special ethical responsibilities

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[1] I thought it best to leave the main text of this essay just as it was when presented in 2001. I have, however, added an epilogue to bring matters somewhat up to date.

Preface

Let me begin by noting how delighted I am to be back at the University of Michigan Medical Center and especially to deliver the sixth annual Raymond Waggoner Lecture. Unfortunately, I was not a personal friend or close colleague of Dr. Waggoner, but I certainly knew a lot about him and the many contributions he made to the Department of Psychiatry, to the Medical School, and The University of Michigan. It is, therefore, an honor for me to have been awarded this lectureship and in some very small way to connect my name to his and, even more indirectly, to the distinguished history of this Department and the University of Michigan Medical School.

Finally by way of prefatory remarks, I want to say a few words about the Medical Center. I have many friends here and I think often about many of them and all they have done and continue to do for the Medical Center and the University. At this particular moment, however, I recall especially those efforts to revitalize the medical center that began over two decades ago and continues to this day. As I think back on those initial struggles I am amazed and enormously gratified by what has been accomplished over this period through the leadership of the current faculty, staff, and administration of the Center and the University. All of us who care deeply about the University, about the welfare of patients and our ethical obligation to push forward the bio-medical frontier, have accumulated a significant debt to all levels of today's leadership in the Medical Center and the University. I hope you will consider my presence here this afternoon as a small down payment on my share of this obligation.

I. Introduction

This annual lectureship has as its focus ethics and values in medicine and in a few moments I will speak directly on one aspect of this rich, diverse and important area. Indeed, there are so many aspects of ethics and values in medicine that it is often difficult to locate the right balance among our various ethical obligations in particular circumstances. This is not because physicians, or other health care professionals cannot be bothered to struggle with moral issues, but because they operate within a highly contextualized and deeply uncertain environment where ethical behavior requires complex moral calculations/considerations. Moreover, at any moment in time there are often competing ethical demands that leave us with difficult, even tragic, moral choices. In addition, there are a lot of ethical issues in medical practice and biomedical research because these activities directly impact the interests of others. Moreover, since the ethical issues that do arise require practical implementation, one has to find ways to cross the chasm that often separates moral theories and ethical practices. Indeed, one of the chief burdens of my remarks this afternoon is that health care professionals engaged in human subjects research cannot escape the moral anxieties that characterize everyone that thinks deeply about behaving in an ethical fashion.

This is certainly the case for investigators involved in research using human subjects since few endeavors have the potential to present more strikingly the tension that can arise between individual and society interests than does medical research involving human subjects. The problems and moral choices you face are not simple

ones and usually raise competing interests. It is understandable, for example, that as we strive to meet our ethical responsibilities to future generations of pushing forward the scientific and clinical frontier, that we may lose sight of other ethical imperatives or, more likely, simply not give them sufficient weight. In this latter respect I think one of the most important ethical lessons of the recent decades is that assigning relative weights to competing moral demands in human subject research is not a matter that can be left to one group, say, physicians, or policy makers, or religious leaders, or human subjects themselves. Rather it must result from a process of social negotiation where all those whose interests are affected have some standing in the deliberations.

This is especially the case now because commercial interests have become deeply embedded in all aspects of biomedical science. Indeed, biomedical science has become a vast commercial activity. This may or may not be a good development, but for many researchers it certainly generates a new and expanded portfolio of actual or perceived conflicts of interest. As a result, the public no longer considers individual self-regulation adequate. In fact, however, it was always difficult to imagine that given the multitude of pressures that physician/scientists work under that they could adequately address the ethical implications of their own work. In my view it has always been unreasonable and unfair to leave all the ethical decision making to the moral sensitivities of the individual medical investigator. Given the various pressures investigators work under, we protect neither subject nor investigator by having a system devoid of meaningful third party oversight.

The ethical considerations involved in medical experiments that involve human subjects is hardly a new topic, but I have chosen to speak about it because I think it is time for some important changes in attitude and regulation/oversight in this arena. I will begin by reminding ourselves of the historical legacy we share in this area (including the status quo) and move on to suggest what changes in attitude, ethical commitments, and principles are necessary to serve more fully, both the advancement of medical science and the protection of human subjects. It is my own strong belief that good ethics can not only mean good science, but is essential to sustain the strong public support upon which all aspects of the bio-medical enterprise are dependent. My emphasis will be on the beginning and the "end" of the ongoing narrative connecting investigators and human subjects, namely, the historical legacy we share in this arena and what I propose for the future.

By way of introduction I want to suggest that there are four key issues relating to our ethical responsibilities to human subjects participating in medical experimentation that arise over and over again. The first is how to most effectively balance the interests of the human subject and those of science and future patients. The second is whether and in what manner the conduct of the investigator should be monitored and/or controlled by third parties. The third is what special arrangements are justified for what may be considered vulnerable populations. Finally there is the issue of how one insures that the experiment is well designed scientifically. This latter concern is one that relates to all research, but it has very special moral salience when human subjects are involved. In my view all the various controversies in the area of medical experiments

using human subjects swirl around attempts to deal with some combination of these four issues. The current regulations, however inadequate and unloved, are an attempt to address these questions in a manner that will protect both investigator and subject. Let me now sketch the general contours of our historical legacy on these matters.

II. The Historical Legacy

Although formal medical experiments were either rare or non-existent in the ancient or medieval world, the historical record does contain some evidence of using slaves, criminals (not quite persons in the moral sense), or even patients for this purpose. By the eighteenth century, however, there are numerous recorded incidents or orphans and/or slaves being used as "human guinea pigs." The term "human guinea pig" was coined somewhat later by George Bernard Shaw, but the use of these particular populations did reflect our lack of full respect for them and our failure to see them as worthy of full moral respect. In one of the most famous clinical trials in this period, however, we see a rather different approach when Edward Jenner vaccinated both his son and another healthy child with cowpox. Even as late as the eighteenth century, however, formal medical experiments were still few in number and, thus, when Thomas Percival published his justly famous "Medical Ethics" in 1803 he has very little to say regarding medical experiments using human subjects.

However, when Claude Bernard, the French physiologist, published his "Introduction to the Study of Experimental Medicine" a half-century later, he was already sensitive to some of the ethical issues involved. He seemed to have believed that since

Christian morality required one not to harm their neighbor, medical investigators would, as an ethical matter, need to restrict their pool of human subjects to those that might benefit from the experimental intervention. On the other hand, he and others at the time had no problem doing medical experiments on condemned criminals since, the argument went, no additional harm could come to them. Earlier William Beaumont a self-described “humble inquirer after truth” had done a whole series of experiments on one Alexsis St. Martin who was bound to Beaumont by a formal indenture. It was not until the end of the nineteenth century, however, that the healthy adult volunteer became an important participant in medical experiments. One of the first of these experiments was the justly famous experiments headed by Walter Reed dealing with the origin of yellow fever.

Whatever the ethical problems may have been during these earlier periods, the rise in experimental medical science that began in earnest in the nineteenth century has transformed both medical practice and medical science. Indeed, one must conclude that the resulting developments in our understanding of human biology, disease and the more effective clinical modalities that have resulted must be considered both an enormous scientific accomplishment and a significant humanitarian achievement. In the last two centuries we have witnessed extraordinary declines in mortality due, not only to better nutrition and improved economic circumstances, but to a combination of public health measures and a large number of new clinical modalities that have enabled us to overcome what previously were often fatal conditions.

Nevertheless, the historical record also reveals that in the general enthusiasm to develop new and more effective clinical modalities some investigators, with or without consent, deliberately infected human subjects, often drawn from what today we would call vulnerable groups, to test various theories. The record shows that as the need for medical experiments grew, many physicians and others treated institutionalized infants, dying patients, and mentally impaired individuals as not quite persons in the moral sense. Moreover, indigent patients in hospitals were often treated in a similar fashion. Indeed, during the last half of the nineteenth century indigent patients and their advocates became increasingly concerned that they were often the unwitting subjects of medical experiments, and the objects of unwanted dissection after death.

Clearly these “vulnerable” individuals were thought of as not quite eligible for the moral consideration we would feel obliged to extend to those who were, in our judgment, full persons in the moral sense. They were, our practices suggested, not entitled to the same rights and respect that others enjoyed. While some of these experiments produced great benefits for succeeding generations and society as a whole, they often involved overlooking the rights and welfare of the human subjects involved.

These matters did not go unnoticed by the medical profession. Ever since the rise in experimental medical science in the latter half of the nineteenth century, some members of the medical profession were quite aware of these tensions and of the variety of ethical issues raised by the use of human beings in medical experiments.

William Osler, for example, suggested that one way to mediate this tension was to insist that animal experimentation be carried out first and that patients should only be involved if a direct benefit to them was likely to follow. Of particular concern to Osler and many other physicians was the preservation of what he termed “the sacred cord which binds physician to patient.” With respect to healthy subjects, Osler, and many others, thought that some sort of consent should be the key requirement.

Given the long history of medicine, and the fact that doctors have always experimented in the treatment of their patients, it may seem surprising to some that the moral tension, or uncertainty regarding whose interests were being served, as between the investigator and subject has come to the fore only relatively recently. The “late” arrival of this issue is, of course, the result of two principal factors. The first is the relatively recent rise of what we would recognize as scientific medicine, and therefore, the whole issue of medical research ethics. The second set of factors, however, is less well appreciated, and I want to take a few moments to focus on it.

These are the new cultural commitments associated with the rise of democratic and pluralistic liberal societies. Most importantly the values underlying the development of these liberal societies brought renewed emphasis and commitment to notions of individual freedom, responsibility, and autonomy. Moreover, these very same cultural commitments released the latent talents of many individuals to try out a wide variety of experiments, not only in science, but with all of society’s institutions. That is, the same forces that were responsible for directing so much human creativity and effort towards

scientific activity also caused us to refine our notions regarding the integrity, autonomy, and value of each individual, and our ethical responsibilities to every individual whose interests are significantly impacted by our actions. Perhaps it should come as no surprise, therefore, that sooner or later the demands of science would come into conflict or tension with our evolving moral sensibilities.

In any case, it is important to remember, therefore, that the two principal cultural commitments of modern times, namely, the active pursuit of our mastery over nature – now including human nature – and the construction of a cultural framework that places a high value on accommodating the multiplicity of individual interests that naturally arise from the wide diversity of individual circumstances, beliefs, and historical contexts, can come into tension with each other. That is, these two great commitments of modern times can, in some circumstances, become competing interests. Unfortunately, medical experiments using human subjects are one example where such a tension may arise, since any scientific activity, no matter how worthy, that undermines the dignity of individuals or devalues them as autonomous moral agents, now creates what one may call a cultural contraction.

We should, however, not despair. There is nothing very unusual about such a cultural contradiction. Often we find ourselves in situations in which there is no way of acting that can satisfy all the ethical requirements to which we are committed. Existing realities often force hard, even tragic, moral choices. Moreover, in a morally pluralistic society such as ours, there are bound to be ethical conflicts that are not due to such

unworthy characteristics as selfishness, prejudice, ignorance, or poor reasoning. In such circumstances our best strategies are to acknowledge the difficulty and to devise plans that enable us to minimize the negative impact on the interests of others of our inability to meet all of our ethical responsibilities. Indeed, existing regulations governing research using human subjects, however bothersome, irksome, and bureaucratic they may seem, need to be understood also as an attempt to manage just such a complex ethical situation.

For reasons that are perhaps understandable, during the nineteenth and first half of the twentieth century reconciling the needs and rights of patients and other human subjects with the growing demands of worthy medical research was not easily accomplished. In particular, consent was a complicated, murky, and often ambiguous feature of medical experimentation until quite recently. Indeed, it is quite understandable given the clinical environment during the late-nineteenth and early twentieth centuries that many well-motivated physicians/investigators saw little wrong with direct or indirect coercion to gain some form of consent. In particular, since benevolent deception and nondisclosure was the clinical norm it was almost “natural” to carry this attitude over to the issue of consent to serve as a subject in a medical experiment. In this respect it is useful to recall that Thomas Percival’s 1803 work on medical ethics, which remained very influential through the first half of the twentieth century, argued that a patient’s right to the truth could be “suspended and even annihilated” in certain circumstances.

Nevertheless, the apparent lack of sympathy for experimental subjects and the clinical detachment with which physicians described experiments on human beings remained a recurrent theme of the debate through at least the middle of the twentieth century. Many of those concerned with the abuse of human subjects continued to associate medical experimentation with the excessive claims of investigators, reckless innovation, quackery and, most importantly, as a new threat to the moral order.

The particular focus of the critics of medical experimentation at that time was on what they believed to be the dubious ethical acceptability of non-therapeutic experiments and on their insistence on the ethical necessity of the written consent of the subjects. The debate, however, often became polemical with groups concerned with animal rights warning over and over again that what we allow today regarding the use of non-human animals in scientific experiments we will allow tomorrow with respect to humans. Indeed, term “human guinea pig” was introduced to make clear the notion that experiments involving the mistreatment of non-human animals was sure to be followed by experiments involving the mistreatment of humans.

For the leaders of the medical profession as a whole, however, especially the elite university-based investigators, any interference with the use of animals for research and teaching threatened the therapeutic promises of scientific medicine. Moreover, on the legislative front, legislators were apparently convinced that any regulation would retard medical progress and inhibit the development of badly needed new clinical modalities. As far as I can tell outside of certain tabloids and the interest of

animal rights groups there was little public concern about the entire issue. Both the public and the Congress perceived little difference between the physician's moral responsibilities when acting as an investigator or when fulfilling their role as a clinician. No one wished to regulate medical practice, and there seemed to be little distinction in most people's minds between the need for oversight in research and the need for such oversight in clinical practice.

As a result, clinical investigators lacked any formal guidelines until the 1940s when the AMA amended their professional codes to require (in a rather vague way) voluntary consent of the subject and prior animal testing. There were, however, no means of oversight or enforcement suggested. Paradoxically, it was Germany (in 1900) that first developed a code of ethics for research protocols that involved experimenting on human subjects. The general theme of this early code was to restrict the pool of human subjects to competent adults who could give fully informed consent. At the same time I must note that there were continuing reports of abuses in Germany through the first three decades of the twentieth century, and new regulations had to be issued in 1931!

Despite the ethical lapses that characterized certain medical experiments during the first five decades of the twentieth century, it did become generally accepted that one should try to avoid unnecessary risks and that voluntary participation was a preferred feature of participation in research protocols. Unfortunately little attention was paid to this latter issue in the case of vulnerable subjects, and oversight responsibilities were

left solely to the moral integrity of the investigator and his/her moral discretion in the implementation of whatever informal guidelines existed.

During World War II, any growing qualms about the inappropriate use of vulnerable populations gave way to patriotic constructions of ethical priorities. Indeed, the lessons that medical researchers may have learned during this period was that ends certainly did justify the means. Abstract moral issues like consent were superseded by a genuine sense of urgency to find clinical modalities needed by the armed forces.

In the two decades that followed World War II and preceded Henry Beecher's exposé of ethical lapses within the American medical research establishment there was an enormous expansion of human experimentation in medical research, but the broad attitudes towards the ethical imperatives faced by clinical investigators remained basically unchanged despite the cessation of hostilities. In short, the two key principles of consent and voluntary informed participation were often disregarded.

Even as the National Institute of Health (NIH) began its enormous expansion, the Clinical Center did little to inform patients to be alert to, for example, the investigator's possible conflicts of interest or to question the researcher closely about the protocol. Instead, they invoked or relied upon the ethos of the traditional doctor/patient relationship and essentially asked human subjects to trust the doctor who was the one most likely to be able to balance the costs and benefits of a particular protocol. As a

result, the Clinical Center set neither formal requirements to protect human subjects nor clear standards for investigators to follow in their protocols.

Further, as the money flowed out of the NIH into the nation's hospitals and laboratories, little attention was paid to the rights and welfare of the human research subjects. While investigators were more and more conscious of their ethical responsibilities to subjects, it was the wisdom and beneficence of physicians that continued to be relied on. In fact many researchers demonstrated little interest in the ethics of research during this period. Research ethics was considered, perhaps, an unnecessary obstacle to progress, and many investigators during these early decades following World War II let themselves slide into non-therapeutic experiments without any form of consent.

In retrospect, it is somewhat surprising that these attitudes persisted despite the Nuremberg trials and the behavior tolerated in many wartime experiments in the U.S. In fact, neither the horrors described at the Nuremberg trial of the infamous Nazi doctors, nor the ethical principles that emerged from it (i.e., the Nuremberg Code) had a significant impact on the American research establishment. The reaction seemed to be that only Nazis needed such regulation and in any case the real problem was the Government (in this case the Nazi government) which had interfered with the medical research agenda. Ironically, only the Department of Defense made the Nuremberg Code the ruling policy for medical experiments using human subjects in the area of atomic, biological, and/or chemical warfare. The problem was that the policy was

classified as “Top Secret” and hardly anyone had access to it or knowledge of it. To most Americans, however, Nuremberg addressed madness, not medicine. Indeed, as late as the 1960s and even after the Thalidomide controversy there was still very little sentiment in Congress to adopt any regulations for the protection of human subjects.

As I noted above, Congress seemed incapable of differentiating either experimentation from therapy or investigators from physicians. To put the matter another way, lawmakers seemed unable to distinguish subjects from patients, or the examining room from the laboratory. In essence, the ethos of the examining room was extended to the laboratory and the trust extended to the physician as healer extended to the physician as investigator. As a result the understandable wish to avoid regulating clinical practice led to a great reluctance to regulate in any way experiments using human subjects. Therefore, investigators ran their protocols free of external ethical oversight. The autonomy they enjoyed in conducting human experiments was limited only by their individual consciences which, as it turned out, was not always sufficient to avoid serious ethical lapses.

All this began to change in the mid-1960s with, perhaps, the publication of Henry Beecher’s article in the New England Journal of Medicine. The ethical lapses that were documented, there and subsequently elsewhere, drew our attention to what should have been the quite obvious tension that could arise within clinical trials between the general good and the rights and welfare of the individual subject between the role of the physician as “healer” and the role of the physician as investigator.

In my judgment, the various revelations regarding abuse of human subjects that began to receive renewed attention in the mid-sixties might have had limited impact on behavior if so much authority and influence with respect to medical research were not concentrated in the NIH and the FDA, organizations that were very sensitive to congressional pressures and public opinion. The most important change in attitude that took place at that time was the public acknowledgement that an inherent conflict of interest arose in the interaction of the investigator and the subject. It became clear that the bedrock principle of medical ethics – that the physician or other health care professional acted only to promote the well being of the patient – did not necessarily hold in the context of research protocols. Instead, and inherent conflict of interest might be expected to cloud the ethical judgment of even very thoughtful investigators.

As a result of both this enhanced sensitivity and continued revelations of ethical lapses, two similar but distinct systems of decentralized oversight were established. One was established by the FDA (for protocols supporting a submission to the FDA) and one by the NIH (for protocols they sponsored). Both of these systems mandated both voluntary informed consent and independent review to ensure a balance of risks and benefits.

From the mid-sixties onward, therefore, the idea that human subject protection required oversight by a disinterested party gradually replaced our complete dependence on the conflicted moral sensibilities of investigators and their staff. Progress in this

area, however, proceeded in stutter-step fashion. It took the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (referred to as the National Commission), which only began its work in 1974, and the subsequent President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (referred to as the President's Commission), appointed in 1974, to construct a coherent, if limited, framework for the protection of human subjects.

The National Commission produced The Belmont Report which articulated the underlying set of principles to support a system of oversight in this arena and a focus on the two key protections needed, namely, informed consent and independent review of proposed protocols. It was the President's Commission, however, that produced the operational guidelines that came to form the basis of the Common Rule (which now governs almost all federally-sponsored human subject research) and the FDA regulations and gave much overdue attention to the protection of vulnerable groups. I should note, however, that it took almost ten years to get the Common Rule adopted by the key federal agencies although the NIH and the FDA moved considerably faster. Thus, it took over four decades from the Nuremberg trials to the effective adoption of a system of oversight and review that attempted to meet the challenge of both protecting human subjects and supporting the continued advancement of medical science.

III. Looking Ahead

I do not want to spend anytime this afternoon outlining the detailed regulations that now govern human subject research. They are well summarized in the Common Rule, its various subsections and the analogous regulations of the FDA. While these regulations may not be loved, they are relatively well known by both IRB members and the community of investigators. Whether successful or not, they are intended to help us all avoid ethically unacceptable research by providing for informed consent and independent review of the balance of costs and benefits. They require that both prospective subjects and a committee of independent peers to conclude that the risks involved are appropriate in view of the potential benefits and provide special protection for vulnerable groups. Moreover, the system is decentralized in the sense that each community of investigators establishes a mechanism to meet the requirements of the Common Rule and/or of the analogous FDA regulations. What, therefore, are the limitations of the current regulations, and why is it time to modify them once again? Let me now turn my attention to those shortcomings that must be addressed if we are to sustain the effectiveness and credibility of the systems.

First, the current system has inadequate coverage in the sense that all human subjects do not fall under the protection of either the Common Rule or the FDA regulations. If neither federal funds nor FDA requirements are involved, there is no system of oversight at all. This leaves an unknown number of investigators and subjects unprotected.

Second, given the vast enterprise that clinical research has become, both IRBs and those involved in system oversight are too overburdened to fulfill their role effectively. Moreover, the typical response to this heavy and under-appreciated workload has been to focus on fulfilling the various bureaucratic requirements rather than on the substantive requirements of their oversight responsibilities. In many ways this is an iatrogenic or self-inflicted problem since nothing prevents an individual institution, or the federal government, from providing greater support for IRBs and those charged with overall system oversight. Simply put, our system of decentralized review is seriously under-resources. No one should be surprised that ethical lapses, even at the most distinguished centers of medical research, continue to occur. Until all partners in the medical research enterprise devote more resources to this effort, no human subject can be assured of appropriate protection. In the long run, failure to address this issue will begin to undermine public support for the entire enterprise.

Third, the critical process of informed consent has become a rather legalistic document-oriented event rather than a serious process of sustaining a meaningful level of understanding between the human subject and the investigating team.

Fourth, even those areas that are covered by existing regulations, there are no single uniform set of requirements or a single source of authoritative guidance to turn to.

Fifth, the current system is so difficult to change that it is unable to adapt to the changing realities of medical science. For example, it deals in a very cumbersome and inefficient way with the increasingly important multicenter trials.

Sixth, the current system ignores the fact that the integrity of a decentralized system depends on the education and training of all those involved on the research enterprise at the local level. Nothing can substitute for the enhanced ethical sensitivity of all those participating in human subject research from the most senior investigator to all other members of the research team. They must not only have a working knowledge of the oversight system, but a clear understanding of the source of their own ethical responsibilities and when they should look for additional guidance. It is my view that no one should become part of a research team unless they have been trained and certified, as appropriate to their responsibilities, in these areas. Such training is not difficult, and both training and certification could easily be made available on the Web.

Seventh, there ought to be a system of compensation for those human subjects that are injured as a result of their participation. While this principle is pretty straightforward, there are many practical difficulties in implementing such a proposal. It is often very difficult to determine if an injury is research-related, and it is not obvious how one should fairly finance such a system. Perhaps compensation could be financed in a manner similar to Federal Deposit Insurance.

Eighth, the entire system and process needs to be more publicly accountable, especially at the local level. There are a number of ways to achieve this. Let me suggest a few. The number of "outside" members of the IRB could be increased. When particular protocols are being considered, especially if they involve more than minimal risk, mechanisms to consult with members of the group most directly impacted should be considered. Such consultations might even improve the experimental design. Alternatively, each IRB could produce a publicly available annual report that described the general nature of its efforts and highlighted the most "interesting," or even the most problematic protocols. Such a report could even provide information on the protocols that were not approved. A different approach to accountability would be to install an audit system of some type that annually would examine a sample of protocols to determine if all appropriate steps had been followed both in the approval and implementation process. I have always thought that a good system of audit could substitute for the constantly increasing number of bureaucratic requirements. Moreover, it would highlight our often overlooked responsibility to monitor the implementation of protocols not just their initiation.

Ninth, we need to reconsider our notions of what we consider vulnerable populations. Although vulnerable individuals need additional protection in research, they should not be arbitrarily excluded from research alone. Generally speaking we consider vulnerable people as those more open to harm (e.g., children), or more subject to coercion (e.g., institutionalized persons). It is important to understand that it is not their group designation that exposes them to injury or coercion, but rather their situation

that can be exploited by ethically unacceptable research. I believe our approach in this arena should not be either to exploit these groups, or to exclude them as subjects, but to search for research designs where members of these groups are not unnecessarily harmed.

Tenth, we need some help from the medical profession to understand somewhat better how we should characterize that “gray zone” that exists somewhere between clinical practice and medical research where innovative and untested medical innovations are being tried out. If a formal research protocol is not involved current regulations do not apply. Further, even if a formal research protocol is involved, if federal funds and/or the FDA are not involved, current regulations do not apply. Nevertheless, in this “gray area” it is uncontested that we have ethical obligations to those patients and/or human subjects that are participants. We need to understand better whether any third party oversight and/or new professional guidelines are needed in this area. We need more forthright discussion and/or guidance on this issue.

Whether or not all these changes are made it is essential that we find a way to provide a far more expeditious review path for a large number of protocols. In particular, we need to define a far more expeditious and less burdensome review path for those protocols that involve only minimal risk. In the same spirit we must find ways to relieve both investigators and IRBs from the review of trivial changes in protocols that are always necessary in the implementation stage of any research trial. To fail to do so simply works to undermine the credibility of the current system which spends too much

effort fulfilling bureaucratic requirements and too little providing meaningful protection of human subjects. Simply put, we need to do a better job of matching the level of protection and review to the level of risk involved.

The ability to do this, however, depends on the training of the investigator and those with authority to expedite or exempt a particular study from review. Education that helps researchers to anticipate and work towards minimizing risks can also greatly expedite the review process. Only by focusing our attention on those studies with a meaningful level of risk or where vulnerable populations are involved can we be assured that the system will deliver substantive protections where needed and not relapse into a bureaucratic maze. It would be much easier to accomplish this badly needed reform, however, if the spirit of the suggestions I have made particularly those dealing with education, certification, and audit were adopted.

No one is more enthusiastic than I am of the continuing potential of medical science, or more appreciative than I am of the great advances announced almost daily regarding advances on the scientific frontier, or more optimistic about what will be accomplished in the years ahead. However, I think it is in the self interest of all those working on this great endeavor to demonstrate to all how much we value and respect those individuals who agree to serve as human subjects especially in risky experiments. Historically, when doctors themselves agreed to serve in this capacity they were rightly thought of as heroes. Now, therefore, we should return the favor by treating those who

agree to participate in our experiments as both heroes and partners in an exciting and morally rewarding joint enterprise.

Epilogue[2]

A great deal has changed in the two decades that have passed since I had the honor of presenting the sixth Raymond W. Waggoner lecture in 2001. Even then twenty years of experience with the Common Rule and the dramatically evolving scientific frontier generated a critical need to re-examine and adapt our approach to human subject protection. Indeed I concluded my 2001 lecture with some modest suggestions regarding needed changes and a more dynamically adaptive system. Since then developments on the scientific frontier both in bio-medicine and information technologies have not only impacted research design in biomedicine but in large swaths of the humanities and social sciences. Moreover the relationship between biomedicine and the social sciences and humanities has deepened and has been aided not only by intriguing developments in the humanities and social sciences themselves, but by the rapid development of particular technologies and suffused in particular by the growing importance of a wide spectrum of new information technologies. It is now widely appreciated that we have a vastly altered research environment that requires the adaptation/expansion of the Common Rule and a reconsideration of some of its requirements. What is required is an amended Common Rule that in the context of our new environment both improves the effectiveness and efficiency of the system while simultaneously enhancing human subject protection.

[2] Added December 2011

In the decade 1885-1995 there were no less than twenty government reports or reports commissioned by the government on various aspects of our system for protecting human subjects with most of these recommending an expansion of coverage and/or a more dynamic and adaptive system. In 2003 a report from the Institute of Medicine called for an expansion of Common Rule protections to all human subjects, better risk-adjusted safety monitoring, addressing financial conflicts of interest, continuing review and adaptation of the system, and acknowledging that the IRBs were most importantly representatives of the interests of the human subjects. In the same year a Government Accounting Office [GAO] report on human subject protection in the Veterans Administration medical centers focused on the need for monitoring and oversight, adverse events reporting, and the appropriate training and support for investigators and IRBs.

While change and adaptation of the Common Rule was needed in 2001 it has now become critical that needed changes be seriously addressed and on July 26th 2011 the U.S. Department of Health and Human Services (HHS) in coordination with the Office of Science and Technology Policy (OSTP) published an advanced notice of proposed rulemaking (ANPRM) regarding changes in the Common Rule.
The foci of the proposed changes in the Common Rule are a set of issues surrounding informed consent, new risk-based protections, new data security and information protection standards, data necessary for system oversight, extension of federal regulations, and harmonizing and clarifying both regulatory requirements and agency guidance.

In the arena of informed consent (including for the use of bio-specimens) the new proposals aim at simplifying forms and broadening the bases for some sort of expedited review and waiver of consent. The emphasis here is on both simplification and the view of consent as a process that is more understandable to human subjects.

With respect to the collection and protection of data the ANPRM proposes mandatory data security and information protection practices that would apply to all potentially identifiable information. These proposals aim at aligning the Common Rule with HIPPA privacy regulations and are especially relevant when dealing with very large data bases. In essence data security would become a necessary condition for research to proceed.

Given the growing importance of multi-site studies the ANPRM contains proposals to streamline the various approval processes. In particular these new proposals suggest a single IRB approval for many of such studies (international trials and FDA-regulated devices still need local IRB approval). Moreover the ANPRM also proposes the re-deployment of IRB resources toward higher risk research by changes in the definition of excused, expedited, and exempt categories of human subject research. These new proposals also require a more systematic approach to the collection and analysis of data regarding adverse events, the collection of data necessary to continually enhance the effectiveness and efficiency of the system as the scientific frontier moves and finally initiatives to clarify and hopefully harmonize regulations and

agency guidance. Finally ANPRM proposes an important but limited expansion of activities covered by the Common Rule.

While this is not the place to launch a full scale evaluation of these new proposals it is perhaps useful to note some of the issues that have been raised. Perhaps the most serious concerns have come from scholars in the humanities and social sciences who are concerned that their access to vast quantities of previously published secondary data might be at risk. In particular they are concerned that the proposed new regulations would not allow them access to identifiable *non-health* related data. For the behavioral and social sciences the secondary analysis of data is critical and they fear the application of the new rules as proposed would prevent access to such data without re-consent etc. Not surprisingly there is also great concern about the lack of clarity in the proposals regarding the requirements for qualifying expedited, excused or exempt status and/or continuing review. In the context of such concerns and others it is important to note that these are proposals and that reactions from the affected communities have been requested. Most importantly HHS has asked for community input on a number of key issues such as when research use of data originally collected for non-research purposes require consent. Are HIPPA standards regarding identifiable and de-identified health related information appropriate for research studies? Should one ever be allowed to re-identify data? Should IRBs be charged with dealing with financial conflicts of interest?

These and other concerns are an important part of an on-going dialog aimed at improving the Common Rule in view of our experience, our values and the changing profile of the scholarly and technological frontier. The important lesson is the most obvious one namely that if our system is to protect the interests of human subjects as well as to promote the development of important new knowledge the system will have to be as adaptive as our evolving values and scholarly interests. It seems to me that this requires two elements that have been missing to date. First would be an on-going evaluation of the system both with regard to compliance and with respect to effectiveness. In this respect I have always been in favor of some sort of randomized audits of IRB operations where the audit report would be publically available. Second would be an institutionalized commitment to constantly update the Common Rule to reflect the evolving values and aspirations of the society in the context of a rapidly expanding scientific frontier.