PRISONERS AS HUMAN SUBJECTS

CLINICAL RESEARCHER REFERENCE GUIDE

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Clinical Researcher Reference Guide

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Purpose of this Reference Guide

This reference guide is for researchers who may conduct clinical research involving prisoners as subjects. This guide is intended to provide clinical researchers with background information, references, and practice pointers for use in identifying and addressing the special and sometimes unique human subject protection issues that may arise in the course of designing or conducting clinical research that involves human subjects who are incarcerated within correctional settings such as jails and prisons. The guide is divided into 5 main sections. The first section addresses prisoners as vulnerable persons. Characteristics about prisoners and prisons that may render prisoners vulnerable as persons, particularly with regard to prisoners as research subjects, are examined.

The second section of this guide provides an overview of the ethical norms and principles that are especially pertinent to clinical research involving prisoners. These ethical norms and principles serve as the foundation upon which research policy and regulation regarding prisoners as subjects of research may be based. Included in the second section is a discussion of the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, and other relevant ethics documents.

The third section addresses the federal U.S. government policy, including regulations, that pertain to prisoners as subjects, such as Subpart C of Title 45 of the U.S. Code of Federal Regulations, Part 46, as well as guidance information provided by federal government agencies, such as the U.S. Department of Health and

Human Services.

The fourth section of this reference guide consists of a glossary of terms that are often used in the context of human subject protections and prisoners as human subjects.

The fifth section consists of Appendices. The Appendices include original source material related to human subject protections and prisoners as human subjects, including material that serves as the ethical and public policy basis for the current scheme of federal policy pertaining to research involving prisoners as human subjects.

A list of suggested readings concludes this reference guide.

Introduction

Clinical research involving prisoners as human subjects may be an important undertaking. Prison populations are characterized by many problems involving the human condition, including poor health status, with the prevalence of many of these problems significantly higher among prisoners than among non-prisoners. Some of these problems are thought to be associated with criminal behavior. Incarceration may in some ways influence the course of these problems, including the outcome of their treatment or intervention. Research may yield valuable information about the nature of the health and well-being of persons who are incarcerated, and perhaps lead to a fuller understanding of particular clinical interventions for these populations.

However, history has demonstrated that research involving prisoners implicates some of the most troubling ethical issues of our time. The forcible use of concentration camp prisoners as research subjects by Nazi (German) scientists and physicians, and the coerced use of prisoners as subjects by U.S. scientists and federal and state governments, are considered among the most egregious cases of widespread abuse of human subjects of research in modern history.

This history has had a profound affect upon the way in which research involving prisoners is viewed by society, and has, in no small part, helped to inform the development of various ethical norms and principles pertaining to human subject protection, including protection of prisoners as research subjects. Not unexpectedly, federal—and to a lesser extent, certain

state laws—now incorporate some of these norms. Nonetheless, these laws and their underlying rationale are not always clear or unambiguous. To complicate matters, their application in practice is often subject to varying interpretation or even misunderstanding. Moreover, guidance for clinical researchers in the use of prisoners as subjects of research is generally lacking or—if available—lacking in specificity. This reference guide is intended to serve as resource to researchers who desire additional information about human subject protection issues related to prisoners as human subjects.

Prisoners as Vulnerable Persons

At first glance, accepting the premise that prisoners are vulnerable persons may be counterintuitive. After all, persons who are alleged or who have been adjudicated by courts to have committed crimes are often considered social pariahs, and thought deserving of punishment, including banishment from society, for conduct that often involves the victimization of others. During the past few decades, the social and political response to crime has been ever more severe: more conduct is criminalized; sentencing to incarceration is increasingly mandatory; terms of imprisonment are lengthier; and release is made more difficult. Our prisons are generally overcrowded. Only occasionally—and clearly not universally—are the most severe of criminal justice practices thought to lack moral value, such as chain-gang labor and capital punishment.

Not unlike their non-prisoner counterparts in the free world, however, prisoners may be vulnerable within the clinical research context, sometimes for similar reasons. For example, prisoners who are minors (such as juvenile offenders), have a terminal disease or who lack decision-making capacity may be considered quintessential examples of vulnerable persons with regard to clinical research. However, these vulnerabilities may be exacerbated by prisoners' very incarceration, and may be extremely difficult to ameliorate. Prisoners may also be vulnerable with regard to clinical research based upon other factors as well, such as the inherently coercive environment of prison settings or prisoners' lack of social support. Factors that contribute to prisoners' vulnerability may

be grouped within the following broad categories:

1. Coercive environment. Among any institutional or hierarchical environment, prisons are considered by many to be among the most coercive. This attribute of prison settings is not unexpected, nor inherently unjust. Large, sequestered populations comprised of persons who may be socio-pathological may under certain conditions require intensive supervision that non-prisoners would for themselves find largely intolerable. Almost every aspect of a prisoner's existence is controlled by prison authorities. This includes, for example, how and with whom prisoners are housed; the hours that prisoners may sleep; when and how prisoners may shower or undertake personal hygiene; when and what foods or drinks prisoners may consume; with whom and how often prisoners may visit or correspond with family or even socialize with other prisoners; when prisoners may see a health professional; and under what conditions prisoners may participate in educational, occupational or other programs.

Prison officials' decisions and rules regarding these and other matters are often immutable, and may sometimes be arbitrary. Prison officials, including prison security staff, generally expect prisoners' strict adherence to rules and prompt compliance with their commands to be unconditional. Prisoners that deviate from these rules and commands can expect to be swiftly disciplined or punished, often with revocation of certain privileges (e.g., preferred housing, job placement, visitation, access to vocational or training programs, etc.) or more restrictive confinement. Prison officials'

broad discretion to take disciplinary action against prisoners is largely protected by law, a fact that is not lost upon prisoners despite the many lawsuits brought against prison officials for abusing such discretion.

Prisoners are also subject to other types of direct or subtle coercion, including risk, threats or acts of physical and even sexual assault from other prisoners or even prison staff. Physical and sexual assault of prisoners by both other prisoners and prison staff is relatively common, and far more prevalent than in the free world. Especially vulnerable to physical attack are prisoners who are mentally or physically disabled, members of disfavored groups, and prisoners who are frail, in poor health or who are diagnosed with diseases or conditions that are stigmatized, such as HIV. Prisoners who are educationally or developmentally disadvantaged, or who are young or new to the prison environment are particularly at risk of physical and sexual assault. Many prisoners with these conditions or characteristics may, to the extent possible, try to conceal their condition in order to avoid the risk or threat of assault. Troubling as the incidence of physical and sexual assault in prisons may be, prisoners are usually reluctant to report their victimization out of fear of retribution, including further assault, and reports suggest that prison officials and security staff often discount or ignore reports of victimization.

2. Poor health status. According to published reports, prisoners as a group are by almost every measure disproportionately in poorer health than are non-prisoners. The prevalence of infectious and

communicable diseases, including tuberculosis, HIV and sexually transmitted diseases, may be several to many times higher among prisoners than non-prisoners. Chronic conditions, such as AIDS-related illnesses and hepatitis C, are also much more prevalent among prisoners than non-prisoners. In certain prison settings, such as jails and other detention facilities, the prevalence of current and lifetime major psychiatric disorders, such as schizophrenia, major depression and bipolar disorder, may be significantly higher than among non-prison populations. Substance dependency, including drug and alcohol dependency, are also much more common among prisoners than non-prisoners. Prisoners who are in poor health may be desperate to obtain treatment for their conditions. Prisoners' poor health may also compromise their decision-making capacity for a host of matters, including matters pertaining to their health and well-being.

An important factor that may compound or even contribute to prisoners' poor health status is inadequate prison-based health care. For many prisoners, especially prisoners who, before incarceration, lacked insurance or the ability to pay, their first or only access to needed health care may be a prison's health service. In the past, inadequate prison-based health care was taken for granted; prisoners with any ailment had essentially no legal recourse to compel prison officials to provided needed health care. But since the U.S. Supreme Court decided in 1976—in the landmark case of *Estelle v. Gamble* (429 U.S. 97)—that governments are obligated under the Eighth Amendment of the U.S. Constitution to provide prisoners with minimally

adequate health care, prison officials have had to grapple with the task of providing health services for an increasingly larger and sickly population. Since the *Estelle* decision, many hundreds of lawsuits have been filed by prisoners against prison officials for what prisoners allege is the failure by prison officials to provide prisoners with health care to which prisoners claim they are entitled. However, in spite of the obligation to provide prisoners with minimally adequate health care imposed by cases such as *Estelle v. Gamble*, courts have generally refused to articulate the precise parameters of the health care that prison officials are required to provide to prisoners under any given circumstance. Instead, courts have left these determinations to the professional judgment of prison health professionals, and some courts have gone so far as to indicate that prison health care need not necessarily even conform to community standards of care.

An important factor that may contribute to inadequate prison-based health care is the lack of suitably trained professional health staff and lack of resources that may be available to prisons. Prisons are difficult settings in which to practice, prison populations are seen as difficult patient populations, and there are few programs for training health professionals to work in a prison health service. The high prevalence of complex disorders and the large number of prisoners with multiple diagnoses, such as Hepatitis C, AIDS-related conditions, mental disability and substance dependency, further confounds the situation. For this reason, recruiting and retaining suitably trained health

professionals to work in prisons is an enormous challenge. Additionally, most states or jurisdictions lack the financial resources to fund prison programs that will provide prisoners with the standard of care for any given ailment, so prison health care may by contemporary standards be considered inadequate.

3. Educational disadvantage. Studies have shown that prisoners lag substantially behind non-prisoners in every measurement of educational attainment and literacy proficiency. In terms of educational attainment, prisoners are far less likely than non-prisoners to have acquired an education beyond the eighth grade, graduate from high school, or gone on to college. In terms of literacy proficiency, prisoners are far less likely than non-prisoners to, for example, attain proficiency in matching multiple pieces of information in a piece of writing; integrating or synthesizing complex or lengthy information; make complex inferences about what they read; or integrate information from dense or lengthy text.

Educational disadvantage may have profound implications for prisoners' capacity to obtain, process and understand basic information and services that may be needed to make decisions about their own welfare. Prisoners may be unaware of or unable to understand simple to complex matters that may affect their health and welfare, and may therefore fail or not understand the need to take steps or to obtain assistance that might help to secure or preserve their health or well-being. For example, intravenous drug users may not understand the nature of their own dependency or

addiction, or the communicable disease risks to their own health or to the health of others posed by sharing needles, even if they understood the legal consequences of illicit drug use. In this case, a program of IV drug treatment or hepatitis C—which is associated with IV drug use—that is not tailored to the educational needs of prisoners who are addicted to drugs may be ineffective.

4. Social support and surrogates. Not unexpectedly, prisoners have greatly diminished social support compared to non-prisoners. Incarceration in almost any prison setting renders most forms of contact between prisoners and their families, relatives or friends highly impractical. Written or telephone communications are restricted and closely monitored; visitation is severely limited, requires advance approval and is otherwise difficult to arrange; prisons are often distantly located from prisoners' homes or families, and usually imposes a tremendous hardship upon families who would visit; and movement of prisoners from prison to prison is common and done with little regard to prisoners' family or social needs. When interactions between prisoners and their families, relatives or friends do take place, the interactions are usually abbreviated, closely supervised and take place in open and public places with little privacy.

A prisoner's history of criminal conduct may also serve to undermine or damage the prisoner's social support, particularly where family members, relatives or friends were victimized by the prisoner. In some of these cases, prisoners may be prohibited from having

any contact with these victims. In these and other cases, prisoners may simply be disowned, or their relationships renounced, by their families, relatives and friends, and these prisoners may have no social support of any kind outside of prison.

The absence of social support for prisoners has important implications for prisoners' welfare, both during incarceration and for release from prison. In non-prison settings, individuals may be able to rely upon their social support network to assist them with an almost infinite range of life's issues, including matters pertaining directly to the individual's own welfare, including work, school, family life, and health. This social support network might consist of close family members such as spouses, partners or children, more distant relations, friends, or even support provided through close community ties such as religious, community or professional memberships. This social support is often considered an important adjunct to an individual's capacity for coping with life's adversities and challenges, and many individuals may defer important life decisions to designated surrogates drawn from their social support network. In stark contrast, prisoners are bereft—justifiably or otherwise—of the emotional support and sustenance that family, relatives and friends are often able to provide. In effect, prisoners may have to make important life decisions in a social vacuum.

5. Other Factors. Other attributes about prison populations suggest that prisoners may be vulnerable with regard to clinical research. First, prison

populations are disproportionately minority. At last report, a majority of prison populations consisted of persons whose race or ethnicity is black, American Indian or Hispanic. The rate of incarceration for blacks and Hispanics is also significantly higher than for whites or Asians, a trend that has consistently increased over the years. Second, prison populations are disproportionately impoverished. Many prisoners have not held jobs at the time of their criminal justice involvement, or were underemployed or homeless. Oddly enough, women, particularly women of color, represent the fastest growing prison population, despite representing just a small percent of the overall U.S. prison population. Hence, research involving prisoners may disproportionately include persons who are socially or economically disadvantaged.

Because of the many attributes or characteristics of prison populations that may render prisoners vulnerable, researchers should be especially cautious when undertaking resarch involving prisoners as human subjects.

Ethical Guidance

Concerns about protecting human subjects of research, particularly in response to well-publicized cases involving the abuse by researchers of vulnerable persons, have culminated in the development over the years of a number of documents or "statements" that set forth principles by which, it is observed, human subject research should be governed. Preeminent among these statements of ethical principles are the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report. While clearly aspirational, these statements of ethical principles have been adopted in whole or in part as the foundation upon which many policies and laws—both within and outside of the U.S.—regarding human subject protection have been based. Where applicable, these principles pertain to human subjects of research regardless of the subjects' status as prisoners. However, in recognition of prisoners' special vulnerability, some of these statements of ethical principles may specifically address prisoners as research subjects. Familiarity with these statements of ethical principles may result in a more thorough understanding of policies and laws pertaining to human subject protection, including how such policies and laws may apply to prisoners as human subjects.

Nuremberg Code

Background on the Nuremberg Code

The Nuremberg Code arose from the post-World War

II prosecution—called the "Doctors' Trial"—of Nazi German scientists and physicians who were charged with the murder, torture and other atrocities committed against thousands of concentration camp prisoners. These prisoners were used by the scientists and physicians as subjects in a broad range of experiments that had military applications, such as trying to understand how high-altitude and cold sea water may affect military personnel. The post-war military tribunal that was prosecuting and judging the scientists and physicians arranged—with the assistance of the U.S. Army and subsequently the American Medical Association—to establish a standard against which the conduct of the scientists and physicians could be measured. This standard was developed by Andrew Ivy, a prominent U.S. researcher who was commissioned by the American Medical Association to serve as a consultant to the prosecutors of the Doctors' Trial, who testified as a witness in the trial, and who prepared a report for the AMA regarding standards for human subject research. The military tribunal apparently placed great weight on Dr. Ivy's testimony and his commissioned work, and in the tribunal's verdict regarding the guilt of many of the scientists and physicians, announced the tribunal's standard for human subject research that later became known as the Nuremberg Code.

Text of the Nuremberg Code

The Nuremberg Code is not by itself a free-standing document, but is included in the decision of the military tribunal in the legal case in which various Nazi scientists and physicians were charged with war crimes. The entire text of the Nuremberg Code is as follows:

THE NUREMBERG CODE*

Permissible Medical Experiments

The great weight of the evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. *All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts*:

The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

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.

The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has

reached the physical or mental state where continuation of the experiment seems to him to be impossible.

. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

*from the *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10.* Nuremberg, October 1946–April 1949. Washington, D.C.: U.S. G.P.O, 1949–1953 (emphasis added).

U.S. Law and the Nuremberg Code

Interestingly, the Nuremberg Code had at one time been adopted as a policy by at least one U.S. government agency—and has since been adopted by at least two courts—as a standard against which U.S. scientists might be held. In 1953, Secretary Wilson of the U.S. Department of Defense included the Nuremberg Code, verbatim, as the official Department of Defense policy applicable to the Army, Navy and Air Force services in a memorandum with regard to "human volunteers in experimental research." Unfortunately, the memorandum was classified as "top secret" until 1975, so its distribution—and perhaps implementation—may have been severely limited.

In two of the most significant legal cases in which research subjects or their survivors sued researchers for allegedly violating subjects' rights, including rights pertaining to informed consent, judges in both a U.S. federal and state court issued legal opinions that essentially accepted the Nuremberg Code as a standard against which researchers could be held responsible. In

the 1995 case of In Re Cincinnati Radiation Litigation (874 F. Supp. 796, Southern District, Ohio), which involved radiation experiments and impoverished patients, Judge Beckwith stated that "the Nuremberg Code is the law of humanity," and that the Nuremberg Code "may be applied in both civil and criminal cases by the federal courts in the United States." In the 2001 case of Grimes v. Kennedy Krieger Institute (782 A.2d 807, Court of Appeals, Maryland), which involved lead experiments involving children in public housing, Judge Cathell stated that "the Nuremberg Code . . . should be the preferred standard for assessing the legality of scientific research on human subjects." While the adoption by courts of the Nuremberg Code as a source for establishing a standard against which researchers' conduct regarding their human subjects may be measured is, to date, very limited, it is noteworthy that the Nuremberg Code continues to have special meaning long after its original intended purpose has been largely forgotten.

Applying the Nuremberg Code to Research Involving Prisoners

With regard to research involving prisoners as human subjects, perhaps the most significant section of the Nuremberg Code is the first clause, which provides in part that, "[t]he voluntary consent of the human subject is absolutely essential." Strictly interpreted, persons who lack the capacity for providing voluntary consent—such as persons who are legally incompetent (e.g., minor children) or persons who, due to a physical or mental disability, are deemed incapable of providing voluntary consent—cannot be involved as human subjects in research, even if consent

might be provided by a legally authorized representative, such as a parent or legal guardian. Under this first clause, research involving prisoners as human subjects may also be foreclosed since prisoners are, due to the coercive environment of prisons, unable to exercise free power of choice for the purpose of making a decision to take part in research. Coercion aside, research involving prisoners as human subjects may, due to their educational disadvantage, also be foreclosed where prisoners lack the knowledge and comprehension of proposed research and are unable to "make an understanding and enlightened decision" about taking part.

Perhaps the optimal case for conducting research with prisoners as human subjects requires researchers to affirmatively and convincingly establish, prior to conducting research, that each and every prospective prisoner subject is able to voluntarily take part in research; has the capacity to understand the proposed research; has actually understood the proposed research; and, of course, has consented to take part in the proposed research. Anything less may render research involving prisoners as human subjects as suspect.

Declaration of Helsinki

Background on the Declaration of Helsinki

The Declaration of Helsinki might be said to be the most widely recognized set of ethical principles around the world, although its relevance to researchers in the U.S. has generally been limited due to the ascendancy of The Belmont Report, at least in this country, and the

promulgation of federal regulations on human subject protection, more about which is described below. The Declaration of Helsinki came into being in 1964 after considerable deliberation and review by the World Medical Association (WMA), which is an international organization comprised of medical professional organizations from 27 different countries. The U.S. is represented in the WMA by the American Medical Association. The WMA was created with the mission of establishing and promoting standards of ethical behavior for physicians the world over.

The Declaration of Helsinki is the WMA's policy statement of ethical principles, and is intended by its drafters to provide guidance to physicians and other participants in medical research involving human subjects. Importantly, the Declaration of Helsinki is widely considered to represent the further refinement and major advance of the principles first laid down in the Nuremberg Code. The Declaration of Helsinki is separated into three sections, with the first section consisting of 9 general rules; the second section consisting of 18 "basic principles for all medical research;" and the third section consisting of 5 additional principles for medical research that is combined with medical care.

Text of the Declaration of Helsinki

The most current version of the Declaration of Helsink may be found by searching the web site of the World Medical Association, which publishes the Declaration of Helsinki and makes revisions from time to time. The entire text of the Declaration of Helsinki is as follows:

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

[Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002 Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004]

Introduction

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

Basic Principles for all Medical Research

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for

the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be

adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects

with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

Additional Principles for Medical Research Combined with Medical Care

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[1]

At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.[2]

The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to

participate in a study must never interfere with the patient-physician relationship.

In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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[1] **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki:** The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

> Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
>
> Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[2] **Note of clarification on paragraph 30 of the WMA Declaration of Helsinki:** The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures

identified as beneficial in the study or access to other appropriate care. 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.

U.S. Law and the Declaration of Helsinki

In the U.S., the Declaration of Helsinki is, as earlier observed, transcended as a body of ethical principles by the Belmont Report, and as a statement of policy on human subject protection, by U.S. federal and state regulations, which are discussed in detail below. However, the Declaration of Helsinki has important relevance to researchers in the U.S. First, unlike the Nuremberg Code, the Declaration of Helsinki has been vetted by an international organization among its many constituents, including the American Medical Association, over a number of decades, and its provisions—including its subsequent revisions—have been subject to careful consideration and critique from among the world's preeminent physicians, scientists and ethics experts.

Second, the Declaration of Helsinki is endorsed as a foundation for human subject protection policy, or actually serves as the *de facto* policy, in many nations around the world, as well as the European Union. Thus, research practice in many places outside of the U.S., including research conducted by U.S. researchers in such places, is expected to conform to the Declaration of Helsinki. Third, as indicated in the above discussion about the Nuremberg Code, some courts in this country have explicitly acknowledged the pivotal contribution that statements of ethics principles have played in helping to establish a legal standard against which researchers could be held responsible for violating the rights of human subjects. For

example, in the Grimes v. Kennedy Krieger Institute case discussed earlier, Judge Cathell observed—before ruling that defendant researchers had violated Maryland state law in an experiment involving children—that courts may adopt "various policy considerations" for imposing legal responsibilities that researchers have to their subjects. For Judge Cathell, included among these policy considerations was the Declaration of Helsinki.

Finally, even the U.S. Food and Drug Administration (FDA) has apparently found value in the Declaration of Helsinki. Its 1997 "Good Clinical Practice: Consolidated Guideline" publication was intended to provide researchers with a "unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects." The guideline provides that compliance with the Good Clinical Practice standard gives public assurance that human subjects will be protected in accord with the Declaration of Helsinki. Interestingly, however, the FDA's 1997 publication included a statement that the guideline "does not create or confer any rights for or on any person and does not operate to bind the FDA or the public," an unmistakable message that the Declaration of Helsinki is clearly aspirational rather than obligatory under FDA regulations.

Applying the Declaration of Helsinki to Research Involving Prisoners

Similar to the Nuremberg Code, concerns about prisoners as research subjects loom large in the history of the Declaration of Helsinki. The abuses visited upon concentration camp prisoners by the Nazi scientists and physicians were invoked by the drafters of the first

Declaration of Helsinki, and provisions that pertain to vulnerable populations and voluntary, informed consent reflect drafters' concerns. With regard to prisoners as human subjects, perhaps the most relevant sections of the Declaration of Helsinki are paragraphs 8, 20, 23, and 24. For example, paragraph 8 addresses the need for special attention for persons who are "economically and medically disadvantaged" or those who "may be subject to giving consent under duress," characterizations that are considered especially suitable to prisoners. Paragraph 20 provides that "subjects must be volunteers and informed participants" in research; in paragraph 23, physicians are instructed that they should be particularly cautious when subjects "may consent under duress." Both paragraph 20 and 23 serve to reiterate concerns about prisons as coercive settings.

Paragraph 24 addresses subjects who are incapable of providing informed consent, which of course may be construed to apply to prisoners: under paragraph 24, such persons "should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot be instead performed on legally competent persons." If paragraph 24 is strictly interpreted, one might conclude that (a) if the research is not required to improve the health of prison populations, then the research should not involve prisoners; and (b) even if the research is required to improve the health of prison populations (a proposition that may be difficult to prove), the research should not involve prisoners if legally competent persons (i.e., non-prisoners) are available as subjects. At first glance the Declaration of Helsinki does not appear as prohibitive as the Nuremberg Code may be interpreted with regard to

consent. However, the Declaration of Helsinki's recurring reference to the protection of vulnerable persons and to the notion of voluntary, uncoerced decision-making by prospective subjects suggests that the use of prisoners as research subjects, in locations where conforming to the Declaration of Helsinki is obligatory, may be a uncertain proposition.

The Belmont Report

Background on the Belmont Report

The Belmont Report is a "statement of basic ethical principles" and related observations developed by a multidisciplinary group of eleven experts who were convened—pursuant to law passed by the U.S. Congress in 1974 under the National Research Act—as the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ("National Commission"). Members of the National Commission were given the specific responsibilities of (1) identifying the basic ethical principles pertaining to biomedical and behavioral research involving human subjects; (2) developing guidelines to help ensure that biomedical and behavioral research would be conducted in accord with these basic ethical principles; and (3) recommending policy action to the Secretary of the *then*-Department of Health, Education and Welfare (predecessor to the current U.S. Department of Health and Human Services).

The Belmont Report is the culmination of the National Commission's work with regard to the first two responsibilities, and in 1978 was provided to the U.S.

President, Congress, and the Secretary. In addition to the Belmont Report, the National Commission prepared a number of reports on other matters under its mandate, including a 1976 report on research involving prisoners. In these reports, the National Commission provided policy recommendations to the Secretary, many of which were adopted and are reflected in the federal regulations that govern much of the research that is federally funded or conducted. To this day, the Belmont Report is regarded as the preeminent statement in the U.S. of ethical principles pertaining to human subject research, and is considered by many to be the foundation upon which federal human subject research policy rests.

The Belmont Report is divided into 3 sections. The first section briefly addresses the special concern about distinguishing research from practice, and when therapy is combined with research. The second section includes a discussion of the three basic ethical principles in human subject research. The third section includes commentaries about applying the three basic ethical principles.

Text of the Belmont Report

The Belmont Report, although released by its drafters in 1978, was published for public review and comment in accordance with federal law in 1979. While it has since been suggested on a number of occasions, there have been no revisions to the Belmont Report. The entire text of the Belmont Report follows:

The Belmont Report

Office of the Secretary*

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.(2) By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that

objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.(3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons

Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished

autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not

be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence

Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to

particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice

Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to

be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes

(e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent

Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information

Most codes of research establish specific items for

disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to

accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension

The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or

not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness

An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable. Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitle.

2. Assessment of Risks and Benefits

The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be

overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague

categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects

Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select

only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the

involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

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(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

National Institutes of Health
Bethesda, Maryland 20892

*AGENCY: Department of Health, Education, and Welfare

ACTION: Notice of Report for Public Comment

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to 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 which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: (i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research and (iv) the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

U.S. Law and the Belmont Report

For reasons that may now be obvious, the Belmont Report may for U.S. researchers be the most significant statement of ethical principles on human subject research. Clearly, the Belmont Report is more relevant than the Nuremberg Code or the Declaration of Helsinki to research

practices in the U.S. Every research institution or organization that is engaged in research that is supported or conducted by the U.S. Department of Health and Human Services (HHS) is required by federal regulations pertaining to HHS (more about which is discussed below under "Federal (U.S.) Policy") to execute an "assurance" agreement with HHS. Under this assurance agreement, a research institution assumes responsibility for protecting human subjects in accordance with a statement of ethical principles. *The HHS Office for Human Research Protections recognizes the Belmont Report as an acceptable statement of ethical principles for this purpose*. Since many other federal agencies which support or conduct research have adopted the same HHS regulation, the requirement for protecting human subjects in accordance with a statement of ethical principles such as the Belmont Report will apply to research institutions receiving support from these other federal agencies.

Applying the Belmont Report to Research Involving Prisoners

Similar to the Nuremberg Code and to the Declaration of Helsinki, concerns about prisoners as research subjects were an important consideration in the background and drafting of the Belmont Report, and the need to protect prisoners from research risks is directly addressed. In their discussion of basic ethical principles, drafters of the Belmont Report cite the use of Nazi concentration camp prisoners as unwilling research subjects as a "particularly flagrant injustice," and an example of an event that served to place questions of justice in the dialogue pertaining to human subject

protection. The drafters go on to state that as a matter of equity and fairness the selection of certain classes of subjects such as prisoners should be scrutinized, ostensibly to ensure that prisoners are not selected because of their "easy availability," "manipulability" or their "compromised position."

In Part C ("Applications") of the Belmont Report, drafters provide some suggestions for putting the basic ethical principles into practice. With regard to the principle of justice and the selection of research subjects, the drafters suggest that some classes of potential subjects—such as prisoners—not be involved as research subjects unless "certain conditions" are met. In this regard, the Belmont Report may be considered less strict than the Nuremberg Code or the Declaration of Helsinki, since under the Belmont Report some limited research involving prisoners as human subjects is unmistakably permissible. Unfortunately, the Belmont Report does not specify under what "certain conditions" researchers may involve prisoners as research subjects, despite drafters' observation that vulnerable subjects, which would include prisoners, "should be protected against the danger of being involved in research solely for administrative convenience, or because these prospective subjects may be "easy to manipulate." Given their congregate, confined status and their dependent relationship, prisoners are a paradigmatic vulnerable population under the Belmont Report.
Partly in response to the Belmont Report and the expressed need to provide vulnerable persons such as prisoners with additional protections with regard to their participation as subjects of research, federal (U.S.) regulations require research institutions to undertake specific precautions when reviewing and conducting

research that may involve prisoners as research subjects. These regulations are the subject of the next section in this reference guide.

Federal (U.S.) Policy

There are a number of sources of federal (U.S.) policy that pertain to human subject protection generally, and to prisoners as human subjects in particular. One source includes laws that are enacted by the U.S. Congress that establish general goals for—or in some way address—the protection of research subjects. Another source includes legal cases in which federal courts render decisions about the responsibilities that researchers and research entities have to protect human research subjects. Finally, another source may include regulations or rules that are issued or codified by federal executive agencies. Individual U.S. states may also have policies that address human subject protections, but these policies are legally distinct from federal policy. Researchers should consult their own institution's legal counsel and IRB to determine what—if any—state laws may apply, as state laws may provide human subjects with additional or more protection than federal policy.

Congressional enactments typically authorize specific federal executive agencies to create, implement and enforce regulations that will put Congressional enactments into effect. Generally, these regulations extend only to those matters over which the specific federal agency has been provided with legal authority. Some Congressional enactments may require changes in current regulations, or revoke or repeal existing regulations altogether. Federal court decisions may also affect how these Congressional enactments or agency regulations are implemented.

Even with regard to health-related matters, federal agencies' legal authority to regulate is often carefully

delineated. For example, it would be unlikely that matters pertaining to the design and marketing of supplemental restraint systems, such as airbags, which are intended to reduce bodily injury in the event of an automobile accident, will require Food and Drug Administration (an agency of the U.S. Department of Health and Human Services) approval. And matters pertaining to the preparation and distribution of meat and poultry products according to standards intended to minimize risk to public health are within the purview of the U.S. Department of Agriculture, rather than the Department of Health and Human Services. In some matters, however, federal agency authority to regulate may overlap: for example, with regard to the use of animals in a study that is funded by the Department of Health and Human Services (e.g., a study involving the cross-species transmission of disease), both HHS and the Department of Agriculture may have authority to regulate the conduct of such research.

An example of a law that serves as a source of federal policy on human subject protection is §289 of Chapter 6A in Title 42 of the United States Code. This law, which was passed by Congress, authorizes the Department of Health and Human Services to issue regulations to require that entities that apply for HHS support to conduct human subject research provide HHS with assurances that such research is reviewed by an Institutional Review Board. The most important and perhaps widely-known federal policy pertaining to human subject protection is derived from this law, and consists of the regulations that have been issued by the U.S. Department of Health and Human Services under Subparts A, B, C and D of Title 45 of the Code of Federal

Regulations, Part 46. These regulations are usually referred to as *45 CFR 46*, and the current version of these regulations was issued in 1991.

Additionally, the Food and Drug Administration (FDA), a branch of the Department of Health and Human Services, has issued separate regulations regarding human subject protection that are specifically applicable to clinical investigations that are regulated by the FDA. Other federal agencies—such as the Bureau of Prisons of the U.S. Department of Justice—may have their own policies pertaining to human subject protection, including research involving prisoners as subjects. Thus, researchers should aware that the entire human subject research enterprise may be subject to different policies on human subject protection. However, in a nod towards uniformity, many federal agencies have adopted Subpart A of 45 CFR 46 as their own policy on human subject protection. Hence, Subpart A of 45 CFR 46 is referred to as the "Common Rule." Researchers should keep in mind, however, that many federal agencies have not formally adopted the Common Rule.

The Common Rule, or Subpart A of 45 CFR 46, as well as Subpart C of 45 CFR 46, specifically address prisoners as human subjects. In addition to these regulations, the U.S. Department of Health and Human Services has published guidance documents and other materials that further relate to prisoners as human subjects. The regulations at 45 CFR 46 and these related materials are the subject of this section of the reference guide.

The Common Rule (Subpart A of 45 CFR 46)[1]

Background on the Common Rule

As indicated earlier, the regulation at 45 CFR 46 is published by the U.S. Department of Health and Human Services, and represents that federal agency's principal policy on human subject protection. The agency has issued other regulations, including Food and Drug Administration regulations, that also address human subject protection issues, but 45 CFR 46 is perhaps—despite what some commentators describe are its many shortcomings—the most comprehensive body of such regulations in the U.S. The Office for Human Research Protections, or OHRP, is the HHS office that is responsible for ensuring compliance with HHS human subject protection policy.

45 CFR 46 is divided into 4 sections: Subparts A, B, C and D. Subpart A, which is also officially referred to as the Common Rule, is the "basic HHS policy" for the protection of human research subjects. As discussed above, Subpart A has been adopted as the human subject protection policy by other federal agencies, including at least 14 agencies in addition to HHS. Therefore, the Common Rule represents the human subject protection policy for these other federal agencies. The other federal agencies that have adopted the Common Rule—and their corresponding policy in the U.S. Code of Federal Regulations—include the following:

Department of Agriculture (7 CFR Part 1c)
Department of Energy (10 CFR Part 745)
National Aeronautics and Space Administration (14 CFR Part 1230)
Department of Commerce (15 CFR Part 27)
Consumer Product Safety Commission (16 CFR Part 1028)

International Development Cooperation Agency, Agency for International Development (22 CFR Part 225)
Department of Housing and Urban Development (24 CFR Part 60)
Department of Justice (28 CFR Part 46)
Department of Defense (32 CFR Part 219)
Department of Education (34 CFR Part 97)
Department of Veterans Affairs (38 CFR Part 16)
Environmental Protection Agency (40 CFR Part 26)
National Science Foundation (45 CFR Part 690)
Department of Transportation (49 CFR Part 11)

Subparts B, C and D represent HHS policy with regard to specific classes or categories of persons for whom HHS has determined must be provided with additional protection from research risks. Additional protection is required for research involving pregnant women, human fetuses and neonates (Subpart B); research involving prisoners as subjects (Subpart C, which is discussed in more detail below); and research involving children as subjects (Subpart D). Subparts B, C and D are not part of the Common Rule, and adoption of the Common Rule by agencies other than HHS does not mean that these other agencies have also adopted Subparts B, C and D. Thus, research that is supported by a federal agency other than HHS—even if the other federal agency has formally adopted the Common Rule—may not be subject to Subparts B, C or D.

Importantly, researchers should also be aware that some research may not be subject at all to the Common Rule or to any part of 45 CFR 46, including research that is not supported, conducted or otherwise regulated by a federal agency, or research that is funded by a federal agency that has not adopted the Common Rule. The lack of a uniform, nationwide policy is often pointed out as a

major weakness in our "system" of human subject protection. In response, some entities, such as state governments, professional organizations, and research institutions, have adopted the Common Rule or even the entire set of regulations at 45 CFR 46 as their own policy for human subject protection, but in these circumstances the different federal agencies lack the formal jurisdictional authority to enforce such policies.

Generally, the Common Rule establishes a framework for the review of human subject research that entities must follow if the entities are subject to the Common Rule. This framework includes, for example, the definition of terms used in the Common Rule, some of which serve to limit the applicability of the Common Rule to certain types of research that might otherwise be subject to the Common Rule; criteria for Institutional Review Board (IRB) membership; criteria for IRB approval of research, including procedures for expediting the review of minimal risk research; and requirements for informed consent. The entire text of the Common Rule is included in the Appendices.

The Common Rule and Prisoners as Human Subjects

The Common Rule includes several references to prisoners[2] as human subjects. The first reference pertains to research involving prisoners and exempt research. Under the Common Rule, at 45 CFR 46.101(b), certain categories of research are "exempt" from the Common Rule, meaning that the Common Rule policy will not be applied by the federal agency to certain types of research activities. In most institutions, research that is determined to be exempt from the Common Rule will not

be subject to full IRB committee review; however, only the IRB may determine what research, if any, is exempt. Examples of research that are exempt from the Common Rule include research conducted in commonly accepted educational settings and that involve normal educational practices, such as instructional effectiveness; and research involving the collection of existing pathological specimens where the specimens are de-identified by an investigator so that subjects' cannot be identified. Research that falls into these exempt categories is thought to present little or no risk to subjects, and therefore not in need of the scrutiny that full IRB committee review might provide.

However, the exemptions do not apply to research involving prisoners (45 CFR 46.101(b), at footnote (1)). Thus, a research study that might otherwise not require IRB review in accordance with the exemption provisions in the Common Rule *must* undergo IRB review if any prisoner (including prisoner information or specimens) may be involved in the study as a human subject. This will include studies in which both prisoners and non-prisoners may be involved as human subjects.

The second Common Rule reference to prisoners is made at 45 CFR 46.111, titled "Criteria for IRB Approval of Research." Section (a) of 45 CFR 46.111 lists seven (7) requirements that must be satisfied as a condition for IRB approval of research. Under this section of the Common Rule, an IRB must determine, for example, that risks to subjects are minimized; that informed consent will be properly documented; and that the "selection of subjects is equitable." With regard to the need for IRBs to determine that the selection of subjects is equitable, this section of the Common Rule also provides that an IRB "should be

particularly cognizant of the special problems of research involving vulnerable populations" such as "prisoners" (45 CFR 46.111(a)(3)).

This reference to selecting prisoners as subjects suggests that an IRB is expected to critically examine how researchers will recruit prisoners as subjects, including who conducts recruitment (e.g., relying upon or using prison or program staff to approach and recruit prisoners) and the types of inducements that may be used (e.g., participant payments; promises of access other goods or services; etc.). An IRB may also be expected to critically examine a researcher's need for prisoners as human subjects, as well as examine whether less vulnerable persons should be called upon to serve as subjects before more vulnerable subjects are selected. For this reason, researchers should consider being carefully prepared to explain and justify the recruitment and selection of prisoners, including the use of prisoners rather than non-prisoners, as subjects.

The third—and probably the most problematic—Common Rule reference to prisoners is also made at 45 CFR 46.111, under section (b). This section states that "when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as . . . prisoners," that "additional safeguards have been included in the study to protect the rights and welfare of these subjects." For research that is supported or conducted by HHS and that involves prisoners as human subjects, the "additional safeguards" that must be included would, intuitively, follow the additional protections provided by Subpart C of 45 CFR 46, compliance with which would be required. Given that many of the requirements under Subpart C reflect the

suggestions provided by the drafters of the Belmont Report in their 1976 report, Research Involving Prisoners, Subpart C appears to be a carefully considered and an authoritative indication of the types of steps that may help protect against research risks that may be particularly acute for prisoners.

However, for research that is NOT supported or conducted by HHS but is supported by another federal agency that has adopted the Common Rule, the meaning of "additional safeguards" is less clear since compliance with Subpart C's additional protections is not required for this research, and since the meaning of "additional safeguards" is not provided elsewhere in the Common Rule. In these circumstances, researchers and IRBs may respond in one of a number of ways to the need for "additional safeguards" for prisoners that is required under 45 CFR 46.111(b). One response may be to ignore Subpart C—since compliance with that subpart is not required—but to devise additional safeguards that are tailored to the study and to the prospective prisoner subject population.

A second response may be to adopt all of the additional protections described under Subpart C. Such a response would appear logical: if the requirements under Subpart C are considered appropriate for HHS-funded or conducted research, then the requirements may be appropriate for research funded by other federal agencies as well. A third response may be to adopt all of the additional protections described under Subpart C and to devise additional safeguards that are tailored to the study and to the prospective prisoner subject population. If either the second and third responses is adopted, an IRB will not need to comply with the administrative provisions

in Subpart C that require notice and/or approval of the HHS Secretary for certain types of research (see text and comments related to §45.305(c) and §46.306(a)(1) of Subpart C below); HHS does not have authority with regard to research that is neither supported nor conducted by HHS, and will not accept such notice and/or provide such approval. Choosing the second or third response would also foreclose a great deal of research that is otherwise not be permitted under Subpart C, such as research that may provide prisoners with no direct benefit and that presents more than minimal risk.

A fourth response may be to selectively adopt some of the substantive protections described under Subpart C. Finally, researchers and IRBs may, as a fifth response, elect to selectively adopt some of the substantive protections described under Subpart C and to devise additional safeguards that are tailored to the study and to the prospective prisoner subject population. Again, because compliance with Subpart C is not required for research that is neither supported nor conducted by HHS, the nature of the "additional safeguards" that are required in the Common Rule under 45 CFR 46.111(b) is currently left to the discretion of IRBs. Researchers should carefully consider the types of risks to which prospective prisoner subjects may be exposed and how these risks can be minimized, then consult their own IRBs to determine what additional safeguards will be required.

Subpart C (Subpart C of 45 CFR 46)

Background on Subpart C

Subpart C of 45 CFR 46—published by the U.S.

Department of Health, Education, and Welfare (predecessor to the Department of Health and Human Services) in 1978—may be the most important law, federal or state, with regard to research involving prisoners as human subjects. Unlike Subpart A, which is concerned with all classes of human subjects, Subpart C is concerned with only prisoners as human subjects. Much of Subpart C reflects the recommendations provided by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in its 1976 report, Research Involving Prisoners.

Subpart C sets forth additional requirements that IRBs must follow when prisoners are involved as human subjects in research that is supported or conducted by HHS. That is, when an IRB reviews research that involves prisoners as human subjects, and the research must conform to Subpart C, the IRB is required to apply the requirements under both the Common Rule and Subpart C. The general effect of Subpart C is a change in IRB review procedures, and a limit on the types of research that may involve prisoners as human subjects. This is discussed in more detail below.

Researchers should keep in mind that in some circumstances, research involving prisoners may be subject to the Common Rule *but not to Subpart C.* This might arise where, for example, the research is funded by either a federal agency (other than HHS) that has adopted the Common Rule, or by a state or private sponsor, but the HHS assurance agreement of the entity with which the researcher is affiliated does not require compliance with Subpart C. Of course, this would also be the case where the entity with which the researcher is affiliated has no assurance agreement with HHS.

Importantly, Subpart C, like the other subparts of 45 CFR 46, is not part of the Common Rule, and Subpart C has not been formally adopted by federal agencies other than HHS as their own policy for providing additional protections to prisoners as human subjects. That said, other agencies may have their own regulations or rules that pertain to research involving prisoners (such as the Federal Bureau of Prisons of the U.S. Department of Justice), but Subpart C is not codified under the regulations that pertain to federal agencies other than HHS, and is therefore not officially applicable to research supported or conducted by these other federal agencies. Thus, Subpart C is not applied as widely as may be the Common Rule.

Text of Subpart C, with Related Comments

Subpart C was published and became effective as a final HHS regulation on November 16, 1978, over 11 months after the proposed regulation was submitted for public review and comment. The final regulation as published in the Federal Register includes the text of the public comments received and the responses of the U.S. Department of Health, Education, and Welfare to the comments. The comments and responses indicate some of the substance of the concerns about how research involving prisoners as human subjects should be regulated by the federal government, and serve to suggest how HHS justifies its regulatory actions in this matter. A copy of the Federal Register publication of the HHS final regulation is provided in the Appendices. The text of Subpart C provided below is taken from the regulations at 45 CFR 46; the Code of Federal Regulations does not

provide the public comments or the responses. Observations related to each section of Subpart C are also provided:

§46.301 Applicability.

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

Observations on Section 46.301

This section provides that only research that is actually conducted or supported by HHS is subject to Subpart C, which distinguishes this section regarding Subpart C's applicability from the corresponding section regarding applicability under Subpart A, or the Common Rule. However, researchers should be aware that any entity may elect to stipulate in their "assurance" agreement with HHS that the entity will apply Subpart C to research involving prisoners as human subjects, regardless of the research funding source (e.g., internal funds, private sponsor, other federal agency, state agency). In this case, the studies of all researchers affiliated with that entity must conform to Subpart C. It is not clear, however, that HHS will require certification and approval as provided for under Subpart C for research that is NOT supported by HHS, as HHS has interpreted this section to limit their responsibility for

review and approval to only research that is supported or conducted by HHS.

This section also makes clear that Subpart C should not be construed by researchers to permit research involving prisoners—even if such research is allowed under Subpart C—if conducting such research would violate state or local law that further limits or prohibits research involving prisoners as human subjects. In other words, where applicable, state or local laws that are more protective of human subjects—including protection for prisoners as human subjects—must be observed by researchers and IRBs. In fact, a number of states either prohibit or restrict research involving prisoners as human subjects, and may prohibit or further limit research that is otherwise permitted under federal law. Researchers should always consult their own institution's legal counsel and/or IRB to determine what state human subject protection laws may apply. Compliance with federal human subject protection laws does not serve to render state laws inapplicable!

§46.302 Purpose.

> Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

Observations on Section 46.302

This section simply acknowledges the concerns that drafters of Subpart C had with regard to the effect that a prison environment may have upon prisoners' ability to provide effective informed consent to participate as human subjects in research, and that Subpart C is intended to respond to these

very concerns. Of course, prison circumstances and each prisoner may differ with regard to the coercive effect of the prison environment, but the requirements under Subpart C are intended to ensure that regardless of prisoners' individual capacity for providing informed consent, a heightened level of protection is accorded to all prisoners who may be asked to consent to take part in research.

§46.303 Definitions.

As used in this subpart:

(a) "Secretary" means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) "DHHS" means the Department of Health and Human Services.

(c) "Prisoner" means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which providealternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(d) "Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Observations on Section 46.303

This section serves to provide definitions to certain terms that are used in Subpart C, which is important particularly with regard to the term *minimal risk*, which is defined differently in the Common Rule, and to the term *prisoner*, which is used several times but not defined at all under the Common Rule.

Under the Common Rule, the term *minimal risk* "means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." While the Common Rule does not describe or lists the types of possible harms or discomfort, the Belmont Report provides that there are many kinds of harms that may be related to research, including those that are physical, psychological, legal, social and economic. This suggests that the term *minimal risk* as used in the Common Rule should be broadly construed to encompass many different types of possible harm.

Under Subpart C, a different definition of *minimal risk* is provided, and this definition is applicable only when that term is specifically used in Subpart C. Oddly enough, the Subpart C definition of the term *minimal risk* refers only to physical or psychological harms, with no mention at all to discomfort. Furthermore, the term *minimal risk* is only used in Subpart C to limit certain types of research involving prisoners as human subjects (see observations related to §46.306 below). Presumably, any other reference to the concept of *minimal risk* other than its specific use under Subpart C does not require using the Subpart C definition. Thus, when applying a Common Rule requirement pertaining to minimal risk in the review of research involving prisoners as human subjects, an IRB should use the Common Rule—not the Subpart C—definition of *minimal risk*.

For example, under section 46.110(b)(1) of the Common

Rule, research that an IRB finds involves "no more than minimal risk" may be reviewed using an expedited review procedure (i.e., the full IRB need not review the research). Provided all Subpart C requirements are satisfied, research that involves prisoners as human subjects may also undergo expedited review under section 46.110(b)(1), so long as the research involves "no more than minimal risk." In this case, an IRB should apply the Common Rule definition of *minimal risk*, which allows an IRB to consider a wide range of possible harms and discomforts. The Common Rule definition of *minimal risk* should be used whenever the concept of minimal risk is applied to research involving prisoners, and the term is not being used as strictly provided for under section 46.306 of Subpart C. Given that prisoners are considered especially vulnerable persons with regard to research, the use of the term *minimal risk* whose definition is any less inclusive under Subpart C than the definition of the term under Common Rule with regard to the types of harms that IRBs must consider does not appear to make sense. For this reason, researchers should take care to ascertain the probability and magnitude of any kind of harm or discomfort—not just physical or psychological harm or discomfort—that may arise from their research so that IRBs may make an informed risk-benefit determination as part of their review.

There are a number of issues with regard to the term and definition of *prisoner*. Both the Common Rule and Subpart C use the term, but only Subpart C provides a definition. While there is no indication that the term *prisoner* might be defined differently—as is the term *minimal risk*—under the Common Rule than it is under Subpart C, a difference in definition is certainly possible and, under some circumstances, could be significant. Ever since Subpart C was first published in 1978, there has been confusion over what the term *prisoner* was meant to include, such as whether the term included persons on parole or probation, persons committed to mental hospitals, and juveniles housed in correctional facilities. In response to some of the confusion, the Department of Health, Education, and

Welfare indicated in 1978 that the definition of *prisoner* under Subpart C is not intended to encompass (1) persons on parole; (2) persons who are voluntarily confined (e.g., voluntarily civilly committed to a mental hospital); or (3) persons who are involuntarily confined as the result of a commitment procedure in which the commitment is not an alternative to criminal prosecution or incarceration in a penal institution.

Today, however, there are many alternatives to prosecution and incarceration, many of which do not involve confinement to a penal facility. For example, a person who is sentenced by a drug court to a drug treatment program for which no confinement in a penal institution is required, but for which participation in the drug treatment program is required in lieu of incarceration, would not appear to be a *prisoner* as that term is used under Subpart C. Under these circumstances, Subpart C will not apply to research involving this individual. However, if the person violates the terms of the drug court's sentence and is subsequently incarcerated, such as being held in a jail pending a court hearing, then the person would clearly be a *prisoner* as that term is used under Subpart C, and the Subpart C requirements will then apply to research involving this individual. In cases where research has already been approved by an IRB and an enrolled subject is subsequently incarcerated, the research may require re-review by the IRB—and perhaps review and approval by HHS—so that the Subpart C requirements may be addressed. If the research involving a subsequently incarcerated individual is not permitted under Subpart C, then the individual must be withdrawn from the study. Because of the potential for delay in IRB and HHS review and approval and the withdrawal of subjects, researchers should carefully consider submitting for Subpart C review any research that involves persons who may be at risk of incarceration and becoming a *prisoner* as that term is defined under Subpart C.

For research that is subject to the Common Rule but not to Subpart C, researchers and IRBs might refer to the Subpart C

definition of the term *prisoner* for determining when the requirement for "additional safeguards" under the Common Rule will apply for research involving prisoners. Alternatively, IRBs and researchers could use a definition of the term *prisoner* that is either broader or narrower than the Subpart C definition, with a broader definition having the effect of extending the additional safeguards required under the Common Rule to a larger class of persons who fit the definition, and a narrower definition limiting the additional safeguards to a smaller class of such persons. With this in mind, researchers may want to consult their IRBs in advance to ascertain how the term *prisoner* will be defined for research that is subject to the Common Rule but not Subpart C.

§46.304 Composition of Institutional Review Boards where prisoners are involved.

> In addition to satisfying the requirements in § 46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:
>
> (a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
>
> (b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

Observations on Section 46.304

> Under this section, two requirements regarding IRB

membership are imposed in addition to those already provided for under section 46.107 of the Common Rule. These additional requirements are intended to minimize potential conflicts of interests that IRB members may have with regard to their review of research involving prisoners, as well as to ensure that prisoners' interests are directly represented through the IRB.

First, under section 46.304(a), a majority of the IRB, exclusive of prisoner members, cannot have any association with any prison that may be involved in research that is under review by the IRB. This requirement would also apply to the "prisoner representative" on an IRB, more about which is discussed below. When Subpart C was first published, the term *association* was used generally, and meant that an IRB member "should not be an officer, employee, agent, or trustee of the prison or have authority over or responsibility for any aspect of prison activities." The drafters of Subpart C also intended to include "remote" associations under this section. Although not specified, these "remote" associations might include, for example: (1) any service or function that an IRB member may be or anticipates providing to a prison (including a prison official or staff member) that is involved as a study site or source of prisoners as subjects; (2) any relationship (marriage, kinship, business relationship, etc.) that an IRB member may have with any prison official or staff member; or (3) any benefit or interest (payment, honor, etc.) that an IRB member may be deriving or receiving from a prison, prison official or prison staff member.

There is nothing to suggest that IRB members' *past* associations are included for purposes of determining whether an IRB member has any association with a prison that may be involved in research that is under review, although certainly a significant past association, such as prior employment as a prison official or professional, could suggest a potential conflict of interest that should be resolved. Importantly, this section does not prohibit *any* IRB member who has an association with a prison that is involved in the research from taking part in the

review of research; rather, this section prohibits such review only if a majority has such an association. If this is the case, a sufficient number of IRB members will have to refrain from taking part in the review so that those with an association to a prison that is involved in the research constitute only a minority of all IRB members taking part in the review.

The second additional IRB membership requirement, section 46.304(b), provides that *at least* one IRB member must be a prisoner or a prisoner representative. This requirement is intended to ensure that prisoners' interests are represented on the IRB during its review of research involving prisoners as subjects. No particular qualifications are required of a prisoner member, which suggests that drafters of Subpart C may have been satisfied that prisoners would be sufficiently qualified to serve on an IRB simply by their status as prisoners, and that no other special qualifications should be imposed upon prisoners in order to serve on an IRB. OHRP guidance suggests that persons who have previously been prisoners may serve on the IRB.

The substitution of a prisoner representative for a prisoner as an IRB member appears to address the concern that IRBs may not be able to secure a prisoner to serve on the IRB to review research that is subject to Subpart C. While such concerns may be legitimate, the difficulty of obtaining a prisoner or a person who was previously a prisoner to serve on an IRB should not be an excuse to dispense with its attempt. Unlike for prisoners however, this section of Subpart C requires that a prisoner representative have the "appropriate background and experience" to serve in that capacity. This requirement may be one way to ensure that prisoner representatives have qualifications that may to prepare them to provide a meaningful contribution in the review of research involving prisoners as human subjects.

However, determining whether a person has the "appropriate background and experience" to serve as a prisoner

representative on an IRB is problematic. Many persons (e.g., prison social workers and counselors, prison educators, prison health care professionals) may have considerable background and experience with regard to prison conditions. Depending upon the research under review (where the research will take place, e.g., jail, juvenile facility, or state prison; subject matter, e.g., drug abuse, sexual disorder, or HIV; or human subject, e.g., minors, adult men, adult women, persons with diminished mental capacity), a prisoner representative may lack the background and experience needed to meaningfully contribute to the IRB's review of the research. Under these circumstances, IRBs may need to consider appointing more than one prisoner representative, or selecting a prisoner representative who is suitably qualified with regard to the specific research under review. Researchers should carefully explain all aspects of their research in order to assist IRBs to determine whether any particular person will be an appropriate prisoner representative.

That said, the U.S. Department of Health and Human Services publishes some guidance with regard to prisoner representatives. Specifically, HHS suggests that "in the absence of choosing someone who is a prisoner or has been a prisoner, the IRB should choose a prisoner representative who has a "close working knowledge, understanding and appreciation of prison conditions from the perspective of a prisoner." IRBs may need to carefully consider the length of time, the capacity, and the nature of the contact with prisoners, in determining a person's qualifications for serving as a prisoner representative. Whether other persons—such as a spouse or close family member of a prisoner—may serve as a prisoner representative is not altogether clear, particularly since such persons may not have the "close working knowledge, understanding and appreciation" that is required under this section. IRBs and researchers should note that the Common Rule does not impose these special IRB membership requirements to research which involves prisoners and that is

subject to the Common Rule but not Subpart C.

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

(1) the research under review represents one of the categories of research permissible under § 46.306 (a)(2);

(2) any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) the risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular

research project;

(5) the information is presented in language which is understandable to the subject population;

(6) adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

Observations on section 46.305

Under this section, duties in addition to those already set forth under the Common Rule are imposed upon IRBs with regard to their review of research involving prisoners as human subjects. First, IRBs must make specific findings before they may approve research involving prisoners as human subjects. Second, IRBs must comply with any other requirement imposed

by HHS. And third, IRBs must certify in writing to HHS that their duties under Subpart C have been fulfilled. Researchers should be especially aware of these additional duties since much of the information required for the IRB to make their findings may need to be provided to the IRB by researchers directly.

As part of their additional duties under 46.305(a), IRBs must make 7 specific findings as part of their review of—and as a condition for—approving research that involves prisoners as human subjects. Making these 7 specific findings is a critical IRB responsibility, one that is carefully scrutinized by HHS for research that is subject to Subpart C. An IRB may not approve research in which any of the 7 findings cannot be made. Researchers may greatly facilitate an IRB's task in this regard by providing information to the IRB sufficient for the IRB to make these findings.

The first finding (46.305(a)(1)) that an IRB must make is that the research under review must fall within one of the four categories of research that is permitted under Subpart C at 46.306(a)(2). The restriction upon the categories of research that may involve prisoners reflects a long-held ethical concern about involving prisoners as subjects in research that holds out no direct benefit—but poses substantial risk—to the prisoner subjects. The four categories of permitted research operate to limit research to studies that present prisoner subjects with no more than minimal risk, or that may provide prisoners with some direct or indirect benefit. Although this first finding must be made by the IRB, researchers should be prepared to provide the IRB with information that would assist the IRB in making this determination. Research that does not fall into one of these four categories is not permitted under Subpart C. More about this requirement and the types of research permitted under Subpart C is discussed in the next section, § 46.306.

For their second finding (46.305(a)(2)), an IRB must determine that the advantages that are offered to prospective

prisoner subjects in return for taking part in the research do not operate to impair prisoners' ability to weigh research risks against these advantages, when reviewed in light of prisoners' circumstances. That is, an IRB is required to assess whether the prospect of offering prisoners some benefit through research—particularly when prisoners may otherwise be deprived of this benefit—serves to unduly influence prisoners' willingness to take part in the research just to obtain the benefit. A useful example might be the offer to prospective prisoner subjects of a participation payment, say $25, for taking part in a brief interview study, when prospective prisoner subjects have no financial means or ways in prison for earning money.

Another example might be the offer to prospective prisoner subjects of standard drug abuse treatment when prospective prisoner subjects otherwise have no access to drug abuse treatment in prison. While an IRB may be concerned about inducements even for non-prisoners, very little may be known to the IRB about the specific conditions in which prisoners actually live, such as prisoners' ability to earn money, prisoners' access to drug abuse treatment, or any other aspect of prisoners' confinement. Researchers should be familiar with these conditions and evaluate how their inducements may affect prisoners' decisions about taking part in their research, as well as be prepared to provide this information to the IRB so that the IRB may make their own independent determination.

For their third finding (46.305(a)(3)), an IRB must determine that the risks that prospective prisoners might accept by taking part in the research are similar to the risks that non-prisoners would accept. The inquiry here is whether prisoners would accept risks that, had they not been prisoners, they would otherwise not have accepted. Prisoners may be willing to accept a higher degree of risk in research due to the prospect of accruing some highly desirable benefit in return for taking part in research, or prisoners may be willing to accept a higher degree of risk in research because the risk is only

marginally—and therefore not materially—greater than the heightened risks of living in a prison environment.

Importantly, in order to assist IRBs in making a determination under this section, researchers should be prepared to identify any research risks that are reasonably foreseeable, taking into consideration prisoners' circumstances and the prison setting in which the research will take place. Such risks may be very different in type, probability or magnitude than if the research did not involve prisoners as human subjects. For example, research that involves subjects' HIV, mental health or sexual history status or condition may pose qualitatively different risks for prisoners than for non-prisoners, including risk of assault by other prisoners if subjects' HIV, mental health or sexual history information becomes known to other prisoners; or risk of isolation or disciplinary action by prison staff if subjects' HIV or sexual history status suggest current sexual activity while incarcerated, and this information becomes known to prison staff. In making this third finding, an IRB must not only identify these risks, but must consider the acceptability of these risks from the perspective of only non-prisoner subjects.

For their fourth finding (46.305(a)(4)), an IRB must determine that prisoner subjects will be selected fairly and without the unnecessary involvement of prisoner officials or other prisoners, and that control subjects are randomly selected. Here, researchers should avoid using criteria that are not scientifically relevant to the research to exclude or include prisoners from taking part in research. Nor should prison officials arbitrarily exclude or include prisoners from taking part in research. For example, a prison policy permitting only prisoners with a sentence longer than the anticipated research project to take part in research would appear to be a reasonable basis for inclusion or exclusion, while the practice of routinely permitting only male but not female prisoners to take part in research in which gender is irrelevant to the research may be considered arbitrary and unreasonable. Researchers and IRBs

should also be concerned about the potential that other prisoners may influence the selection of subjects through intimidation; both researchers and IRBs should carefully evaluate the means by which prospective subjects are recruited and screened, particularly where prisoners' sensitive and potentially stigmatizing information may be used in the research.

The fifth finding (46.305(a)(5)) that an IRB must make is determining that information about research that is provided to prisoners is done in language that *prisoners* can understand. This requirement pertains to all information, whether in oral or in written form, that may be provided to prisoners, including consent information and consent documents, as well as research study-related information and documents (instructions, follow-up, FAQs, etc.). In order for an IRB to make this finding, researchers should provide the IRB with all documents that may be provided to prisoners, as well as all documents from which material will be orally provided to prisoners. Because the determination of what language will be "understandable to the subject population" will be subjective, an IRB may need to request—and researchers should be prepared to provide—information about the literacy skills and educational attainment of the prisoner population from which subjects will be drawn. This information may usually be obtained from a prison's education program office. By almost any indicator, prisoners have significantly poorer literacy skills and educational attainment than non-prisoners, so the use of materials and documents that have been developed for research involving non-prisoners may be inappropriate for research involving prisoners. Researchers should tailor all information and documents to the literacy skills and educational attainment of the prisoner population from which prospective subjects will be recruited and drawn, and inform IRBs that this has been done.

The sixth finding (46.305(a)(6)) that an IRB must make is determining (1) that a parole board will not, for purposes of

rendering a decision about parole, take into consideration that a prisoner takes or has taken part in the research as a human subject; and (2) that prospective prisoner subjects are clearly informed that taking part in the research will have no effect on their parole. This section is essentially intended to ensure that prisoners' decisions to take part in research are not influenced by the prospect that taking part—or perhaps not taking part—in research will effect any parole decision.

The requirements under this section reflect some of the concerns expressed in the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research's 1976 report, Research Involving Prisoners, in which many of the prisoners involved as subjects in the studies that were then examined were provided with promises of favorable parole decisions in exchange for their participation. Significantly, the drafters of Subpart C indicated that this section is "concerned only with considerations given to the *physical act of participating* in research in relation to parole board decisions," and that the regulations require adequate assurance that "parole boards not consider a prisoner's *participation in research as a criterion* for or against parole" (emphasis mine).

This section requires an IRB to determine that steps are taken by the researcher to ensure that prisoners are not required—as a parole board's condition for making a parole decision—to take part as subjects in research, and that researchers *tell* prisoners that they are not required to take part as subjects in research as a parole board's condition for making a parole decision. This section does not require an IRB to ensure that other information about a prisoner's participation in research (e.g., the fact that a prisoner actually took part as a subject in research, or the type or duration of research in which a prisoner took part) is not disclosed to a parole board.

In practice, IRBs and researchers may actually have very

little control over whether a parole board will or will not consider a prisoner's participation as a human research subject for purposes of making a parole decision. Parole boards have access to a wide range of information pertaining to prisoners—including information about prisoners' activities while incarcerated—for purposes in making parole decisions. If prison records include *any* information about a prisoner's participation in research, this information will be available to prison officials and may be available to parole boards. Furthermore, no law applicable to parole boards serves to prohibit parole boards from requesting or receiving information about prisoners' participation in research.

Additionally, prisoners may themselves want to provide parole boards with information about their participation in research in order to improve the chances for a favorable parole decision. For example, information about a prisoner's participation in a prison-based drug treatment study may be considered by prisoners as important for a parole board to consider when deciding whether the prisoner should be released. This information may be readily available to parole boards, or prisoners may feel that a favorable parole decision would be more likely if such information were provided to their parole board. Under these circumstances, IRBs and researchers have no authority or even means for preventing prisoners from providing this information, or preventing parole boards from requesting this information from prisoners. Ironically, there is a risk that prisoner's unsuccessful participation in research—e.g., failure to complete a drug treatment program that includes a research component—may be considered unfavorably by a parole board, with the result that release on parole may be denied or revoked.

In helping an IRB make the sixth finding, researchers may want to consider (1) withholding from prison officials and staff information about a prisoner's participation in research, (2) asking prison officials and staff not to place such information in a prisoner's records, or (3) obtaining

documentation or evidence that indicates that prison officials or parole boards will not consider a prisoner's participation in research as a criterion for or against parole. Researchers must also indicate to the IRB's satisfaction that researchers will tell prospective prisoner subjects in plain and obvious terms that they are not required, as a condition for a parole board's decision whether or not to award parole, to take part in the research.

The seventh finding (46.305(a)(7)) that an IRB must make is determining whether prisoner subjects may—after their participation in the research has ended—require any follow-up examination or care, regardless of the type of research. If so, an IRB must then determine whether researchers have made plans to provide such follow-up examination or care; whether these plans are based upon each prisoner's sentence; and whether prisoner subjects will be told of these plans. This finding will require researchers to anticipate each individual prisoner's potential need for follow-up care and examination after the prisoner's participation in research has ended, regardless of how such participation will end (e.g., a prisoner's withdrawal from research; the termination of research by the researcher, research entity, sponsor or by prison officials; scheduled end of the research project). Researchers will need to know each prisoner's time remaining in prison, since this may affect the plans for follow-up examination and care (and since this section requires that such plans take into account each individual prisoner's sentence length).

Importantly, researchers will need to actually provide IRBs with the plans for follow-up examination and care, and indicate to the IRB how information about follow-up care and examination will be conveyed to prisoner subjects. The IRB is required to evaluate these follow-up plans to determine whether the plans are adequate, as well as evaluate researchers' provisions for informing prisoner subjects. Researchers should consider contacting their IRB to understand exactly what the IRB will require as to the detail

and the substance of these follow-up examination and care plans in order for the IRB to make this seventh finding.

Apart from the seven findings above that IRBs must make under 46.305(a), IRBs have other duties under 46.305 as well. Under 46.305(b), for example, IRBs must comply with any other requirement imposed by HHS. These other requirements might be included in any directives or instructions issued by HHS, and might be provided at any time. An IRB may have to convey these requirements to researchers in the event that researchers must take any immediate action to comply with such requirements, such as providing the IRB or HHS with additional information about a specific study involving prisoners as human subjects. Additionally, under 46.305(c), IRBs must certify in writing to HHS that their additional duties under this section have been fulfilled, and this certification must be provided in the form and manner (e.g., format, within a specified period of time, etc.) that is required by HHS. Generally, researchers are not directly involved with this specific IRB responsibility, but researchers should be aware that in providing this certification to HHS, an IRB will be relying upon information provided to the IRB by researchers, and that HHS may request copies of this information for purposes of conducting their own review of the research.

§46.306 Permitted research involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:

(1) the institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under § 46.305 of this subpart; and

(2) in the judgment of the Secretary the proposed research involves solely the following:

(A) study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(B) study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(C) research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the **Federal Register**, of his intent to approve such research; or

(D) research on practices, both innovative and accepted, which have the intent and reasonable

probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the **Federal Register**, of the intent to approve such research.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Observations on section 46.306

This section establishes the four categories or types of research that are permitted under Subpart C. Similar to section 46.305(c) described above, this section also requires that an institution provide written certification to HHS whenever the institution's IRB has approved research under section 46.305(c). Researchers should note that research that is supported or conducted by HHS may involve prisoners as human subjects ONLY if the research falls within one of these four categories.

The first category of permissible research (46.306(a)(2)(A)) includes studies of the possible causes, effects, and processes of incarceration, as well as studies of the possible causes, effects, and processes of criminal behavior, but only if these studies pose no more than minimal risk and no more than inconvenience to the subjects. The use of the term *minimal risk* under this section must reference the Subpart C definition,

which was explained above. This category is fairly straightforward, and might include survey, questionnaire or data research that explores whether imprisonment lowers the risk of re-offense, how economic or educational disadvantage may contribute to criminalized conduct, or the effect of inactivity upon prisoners' health, *so long as these studies present no more than minimal risk* (e.g., subjects' identities and responses are confidential; collected data includes no stigmatizing or highly sensitive information; or interaction with prisoners involves no intervention or bodily manipulation). This type of research was actually encouraged by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in its 1976 report, Research Involving Prisoners, because the inadequacies of prisons and their effect of prisoners could itself be an object of research.

The second category of permissible research (46.306(a)(2)(B)) includes studies of prisons as institutional structures or studies of prisoners as incarcerated persons, but—as with the first category—only if these studies pose no more than minimal risk and no more than inconvenience to the subjects. Again, the use of the term *minimal risk* under this section must reference the Subpart C definition. Like the first category of permitted research, this second category is fairly clear-cut, and might include survey, questionnaire or data research that collected descriptive information about prisons or prisoners (e.g., demographic information, population statistics, offense classification, types and prisoner participation in prison programs, etc.), *so long as these studies present no more than minimal risk* (e.g., subjects' identities and responses are confidential; collected data includes no stigmatizing or highly sensitive information; or interaction with prisoners involves no intervention or bodily manipulation). As with the first category of permitted research, this second type of research was actually encouraged by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Studies in the first and second categories of permitted research appear to raise few concerns related to the use of prisoners as

subjects of convenience, and about the inequity of burdening prisoners with research risks without much prospect of benefit.

The third category of permissible research (46.306(a)(2)(C)) includes research on conditions that particularly affect prisoners as a class. Unlike the first and second categories, research in this category *may pose more than minimal risk* to prisoner subjects. However, approval of the HHS Secretary is required before *any* research in this category may be undertaken, regardless of risk. Conditions that are especially associated with prison populations include the obvious, such as certain criminalized behaviors (e.g., psychiatric disorders resulting in homicidal acts or violence to other persons or property; sexual deviancies resulting in rape or other sexual assault; etc.). Other conditions that particularly affect prisoners as a class might include conditions that are much more prevalent among prisoners than among non-prisoners; these include conditions already listed in this section (e.g., hepatitis, alcoholism, drug addiction), as well as other conditions such as tuberculosis, learning disabilities, certain sexually transmitted diseases, severe mental illnesses, and some cognitive disorders. Conditions that may be common to prisoners as well as to non-prisoners would probably not fall into this category of research, unless the course, intervention or outcome of these conditions were significantly different from prisoners compared to non-prisoners. Researchers should be prepared to provide their IRB with sufficient evidence or documentation that research proposed under this category clearly involves a study of a condition that is particularly associated with prison populations.

The fourth category of permissible research (46.306(a)(2)(D)) includes research on practices that are intended to improve an individual prisoner's health or well-being,[3] as well as have a reasonable expectation that such practices will be successful. As with the third category, research in this category may pose more than minimal risk to prisoner subjects. Approval of the HHS Secretary is required

before such research may be undertaken, *but only for research in which prisoners will be assigned to control groups in which prisoners may not benefit from the research*. HHS Secretary approval will be required even if only one prisoner among other prisoners is assigned to a control group may not benefit.

This category of permitted research may be the most difficult to interpret. Obviously, if the research has no control group, then HHS Secretary approval is not required. Similarly, if the research has a control group but no prisoner will ever be assigned to the control group, then HHS Secretary approval is not required. However, it may be extremely difficult for researchers to claim—and a difficult conclusion for an IRB to reach—that a prisoner will not ever be assigned to a control group, especially where researchers will be blinded to the randomization of subjects, and when—for some types of research, non-prisoner controls may subsequently become prisoners (e.g., non-prisoner controls in a drug treatment study get arrested and jailed).

The more difficult case may be where the research has a control group to which prisoners may be assigned, but all prisoners assigned to the control group arm *will benefit*; strictly interpreting this section of Subpart C, HHS Secretary approval should not be required. Once again, however, making absolutely certain that all prisoners who are assigned to a control group arm will actually benefit from their assignment to the control group may be extremely difficult for researchers to claim, and a difficult conclusion for an IRB to reach, particularly where researchers will be blinded to the randomization of subjects.

Also difficult will be assessing how a prisoner will benefit from assignment to a control group. In making this determination, researchers and IRBs must reference section 46.111(a)(2) of the Common Rule, which provides that in evaluating benefits, IRBs should consider only those benefits "that may result from the research," as distinguished from

"benefits of therapies subjects would receive even if not taking part in the research." Thus, in research where prisoners will benefit from assignment to a control group and these benefits are derived from services or treatment that the prisoners would NOT have received without having been involved in the research as human subjects, then approval from the HHS Secretary may not be required. However, where the benefits are derived solely from services or treatment that the prisoners would have received without having been involved in the research as human subjects, then such research will require HHS Secretary approval. Where there is any uncertainty, HHS Secretary approval should be sought.

Finally, researchers should be alert to the possibility that their research project may sometimes include studies that might fall into more than one category under section 46.306(a)(2), and that when this occurs, IRBs should be so informed. For example, research may involve studying prisoner suicide screening among different prisons, and testing the effectiveness of providing a newly-developed prison suicide prevention program in some of these prisons. Such research may fall under the first category of permitted research, 46.306(a)(2)(A), where the study of suicide screening may be characterized as a study of the processes of incarceration; the research may also fall under the fourth category of permitted research, 46.306(a)(2)(D), where the study on the effectiveness of a new suicide prevention program could be characterized as a study of practices that have the intent and reasonable probability of improving the health or well-being of prisoners.

In cases where a research project may fall into more than one category of research under section 46.306(a)(2), the requirements for each category may have to be satisfied. Thus, using the example above, the study of prisoner suicide screening among different prisons—which may fall into the first category of permitted research, 46.306(a)(2)(A)—must present no more than minimal risk to the prisoner subjects. The study of the effectiveness of a new suicide prevention

program—which may fall into the fourth category of permitted research, 46.306(a)(2)(D)—must be designed to improve the health or well-being of prisoners, and must be reasonably expected to succeed; if any prisoner might be assigned to a control group in which a prisoner may not benefit (e.g., assignment to a control group that consists of the standard suicide prevention program that would be available to the prisoner had the prisoner not been involved in the study), then the research must be approved by the HHS Secretary.

Other Policy Matters

In addition to the federal regulations discussed above, there are other sources of federal policy that specifically address prisoners as human subjects. These include the HHS Waiver applicable to Subpart C, and the regulations published by the U.S. Department of Justice that apply to its Bureau of Prisons. Each is briefly discussed below, with the copies of the official policies included in the Appendices.

HHS Waiver Regarding Subpart C

On June 20, 2003, the U.S. Department of Health and Human Services published notice in the Federal Register about a new policy[4] pertaining to a waiver regarding Subpart C regulations. The Secretary is authorized under HHS regulations under 45 CFR 46 to "waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy." Under the 2003 waiver, select provisions of the HHS

regulations under Subpart C are no longer applicable to certain types of research that involve prisoners. This new waiver policy went into effect on June 20, 2003, and permitted IRBs to apply the waiver to any new or continuing research reviewed by IRBs after that date.

The waiver concerns two provisions of Subpart C:

- Section 46.305(a)(1) (which requires IRBs—in their review of research that is subject to Subpart C—to find that research under review falls into one of the four categories of permitted research); and,

- Section 46.306(a)(2) (which essentially requires the HHS Secretary—after receiving certification from an institution that its IRB has approved research under 46.305—to affirm that the research does indeed fall into one of the four categories of permitted research).

Under the waiver, the two Subpart sections above do not apply to epidemiological studies that are supported or conducted by HHS, and that meet the following criteria:

- the sole purpose of the research is to describe the prevalence or incidence of a disease by identifying all cases, or to study potential risk factor associations for a disease; and,

- the institution responsible for the conduct of the research certifies to OHRP (HHS) that the IRB approved the research and fulfilled its duties under section 46.305(a)(2)-(7), and determined and well as documented that the research posed no more than minimal risk and no more than inconvenience to the prisoner subjects, and

that prisoners are not a particular focus of the research.

Oddly enough, the waiver makes little sense, since a reasonable interpretation of Subpart C at section 46.306(a)(2)(B) suggests that epidemiological research may be precisely the type of study of *prisoners as incarcerated persons* that would otherwise be permitted under that section. Nonetheless, the waiver now clearly permits certain epidemiological research that involves prisoners as human subjects, and dispenses with the requirement imposed upon both IRBs and the HHS Secretary from making the determination that such research falls within one of the four permitted categories of research. Researchers should note, however, that *all other provisions of Subpart C must be satisfied* before research that is permitted under the waiver may be undertaken. A text copy of the waiver is provided in the Appendices.

U.S. Department of Justice, Bureau of Prisons (28 CFR 512)

The U.S. Department of Justice is one of the other federal agencies besides HHS that has adopted the Common Rule in its entirety, and this regulation may be found at Title 28 of the Code of Federal Regulations Subpart 46. Thus, the issues and concerns under the Common Rule that are related to research involving prisoners and that are discussed above also apply to the Department of Justice.

Additionally, the Department of Justice has published Subpart B to Title 28, which is found at Title 28 of the Code of Federal Regulations Part 512. Subpart B of

Title 28 applies to research that may involve the staff or prisoners of the Bureau of Prisons, which is part of the Department of Justice. Subpart B of Title 28 imposes additional requirements upon researchers with regard to the review, approval and conduct of research involving Bureau of Prisons staff or prisoners as human subjects. Most of the additional requirements pertain to administrative matters, such as the content of research proposals and requirements for local prison facility and central Bureau of Prisons IRB review. There are also a number of specific requirements that pertain to informed consent.

However, there are a number of provisions under Subpart B of Title 28 that merit special attention. First, under section 512.11(a)(3), research involving Bureau of Prison prisoners may not involve medical experimentation, cosmetic research, or pharmaceutical testing. In this regard, Subpart B of Title 28 would operate to prohibit research that might otherwise be permitted under both the Common Rule as well as Subpart C of Title 45. On the other hand, Subpart B of Title 28 may be less restrictive than Subpart C with regard to permitted research involving prisoners. Other than the restrictions noted above under section 512.11(a)(3), research involving Bureau of Prison prisoners is not limited to one of the four Subpart C permitted categories of research. Conceivably, research may involve Bureau of Prisons prisoners even where, for example, the condition under study does not particularly affect prisoners. Additionally, studies of the causes, effects, and processes of incarceration, and of criminal behavior, or studies of prisons as institutional structures or of prisoners as incarcerated persons, may—under

Subpart B of Title 28—pose *more than minimal risk* to prisoner subjects, so long as such risks are minimized and reasonable in relation to anticipated benefits. This is not the case under Subpart C, under which such research must not pose more than minimal risk or more than inconvenience to prisoner subjects.

Second, Subpart B of Title 28 prohibits researchers from offering Bureau of Prison prisoners with incentives, other than soft drinks and snacks to be consumed at the research setting, to help persuade prisoners to take part in research. This would appear to be more restrictive than Subpart C, under which section 46.305(a)(2) incentives may be permitted, so long as these incentives are not of such magnitude that prisoners' ability to weigh research risks against the possible advantages that will accrue to prisoners is impaired.

There are other additional requirements under Subpart B of Title 28, many of which are unique to the Department of Justice and its Bureau of Prisons. Researchers contemplating research involving prisoners who are under the jurisdiction of the Bureau of Prisons should reference these regulations. Research that is conducted or supported by the Department of Justice, and that involves prisoners that are not under the jurisdiction of the Bureau of Prisoners, will not be subject to Subpart B of Title 28, but must still conform to the Common Rule, which for the Department of Justice is found at 28 CFR 46. Researchers should note, however, that research that involves Bureau of Prison prisoners and that is supported or conducted by HHS would be subject to *both* Subpart C of Title 45 and Subpart B of Title 28.

A text copy of 28 CFR 512 is provided in the Appendices.

[1] All citations to the Common Rule will reference the HHS version of the Common Rule, at 45 CFR 46.

[2] The term *prisoner* is not defined under the Common Rule, although a definition is provided under Subpart C of 45 CFR 46, which is discussed later. The use of the term *prisoner* under the Common Rule could reference the term's definition under Subpart C, but there is no regulatory requirement to do so if the research is only subject to the Common Rule and not subject to Subpart C. The distinction is important, since for some the definition of the term *prisoner* under Subpart C may be seen as either overly or not sufficiently restrictive.

[3] It is possible that some practices, while not improving a prisoner's health, may improve a prisoner's well-being, but the regulations, related comments and HHS guidance do not address this issue. With this in mind, researchers should be prepared to make a strong case that such practices are solely intended to improve each prisoner subject's well-being, and that such practices are *more than reasonably expected to be successful*.

[4] The new policy is titled "Waiver of the Applicability of Certain Provisions of Department of Health and Human Services Regulations for Protection of Human Research Subjects for Department of Health and Human Services Conducted or Supported Epidemiological Research Involving Prisoners as Subjects," and was published in Volume 68(119) of the Federal Register on June 20, 2003, pages 36929-36931.

Glossary

45 CFR 46 (or Title 45 of the Code of Federal Regulations, Part 46)—refers to the body of federal regulations that pertain to the U.S. Department of Health and Human Services ("HHS") (which includes the National Institutes of Health (NIH) and the Office for Human Research Protections (OHRP)), and whose subject matter covers the protection of human subjects for research that is conducted or supported by HHS.

Belmont Report—One of a number of reports prepared in 1978 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, as mandated by federal law; the Belmont Report was intended to serve as a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research involving human subjects. The report was also published by HHS in 1979.

Code of Federal Regulations (or CFR)—an annual U.S. federal government publication which contains the cumulative regulations of the various federal executive agencies.

Common Law—laws that are derived from judicial (court) decisions rather than laws that are derived from statutes or constitutions.

Common Rule—a section of the federal regulation at 45 CFR 46 Subpart A, which some other federal executive agencies (but not all!) have adopted as their

own regulation pertaining to the protection of human subjects of research; the Common Rule can be found in the published regulations of these other federal agencies. Subparts B, C and D of 45 CFR 46 are not included in the Common Rule.

Declaration of Helsinki—a statement of ethical principles established by the World Medical Association in 1964, subsequently revised a number of times, that is intended to provide guidance to physicians and others who conduct human subject research.

Exempt research—research activities involving human subjects that are not subject to certain federal requirements, such as IRB review; categories of research that are considered exempt are identified at 45 CFR 46.101(b)(1) through (6). IRB officials may still decide to subject to their review any research that is otherwise exempt. Research that involves prisoners and certain other vulnerable populations is excluded from exempt research.

Good Clinical Practice Guidelines—a guideline prepared in 1996 by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (or ICH), and intended to provide, in part, a unified standard for designing, conducting, recording, and reporting clinical trials that involve human subjects; in 1997, the U.S. Department of Health and Human Services, Food and Drug Administration, published the ICH's Good Clinical Practice Guidelines, with the intention of publicizing the FDA's "current thinking" on

good clinical practices.

Informed consent—a process during which researchers discuss a research study with a prospective participant. The goal of the process is to provide a prospective participant with information about study in order for the prospective participant to make a fully informed decision about taking part in the study. An informed consent document helps to guide this discussion and provides written information about the study. Generally, the informed consent document is signed by the prospective participant if he or she (or if permissible, a legal guardian acting on behalf of and at the direction of the prospective participant) decides to take part in the study. Some institutions require the principal investigator of the study and the person who is consenting the prospective participant to sign the consent document as well.

IRB (or Institutional Review Board)—a committee of persons established in accordance with ethical principles, and specifically with 45 CFR 46, to provide initial and continuing review of research.

Minimal risk—Under the Common Rule, a risk is considered minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests; for example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so

as part of routine physical examination (Note: the definition of minimal risk for research involving prisoners differs somewhat, as discussed in the reference guide).

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research—a panel comprised of experts representing different disciplines, established in 1974 under federal law (National Research Act, Public Law 93-348), and charged with, in part, developing guidelines for the conduct of research involving human subjects, and for making recommendations for administrative or legislative action for applying such guidelines to research conducted or supported by the U.S. Department of Health, Education and Welfare (forerunner to HHS); the National Commission issued a number of reports (including the Belmont Report and Prisoners as Human Subjects) that included findings, guidelines and recommendations.

Nuremberg Code—a statement of basic principles pertaining to human subject research, developed by Andrew Ivy and Leo Alexander, and used by Allied prosecutors in 1947 in the Nazi war crimes trials involving physicians and scientists who conducted research involving concentration camp prisoners.

OHRP (or Office for Human Research Protections)—a branch of the U.S. Department of Health and Human Services (HHS) established in 2000 to replace the HHS Office for Protection from Protection from Research Risks, and charged with, in part, developing and

monitoring compliance with HHS regulations for the protection of human subjects in research conducted or supported by any HHS component.

Regulation—a federal or state executive agency or local government rule or order that has the force of law.

Statute—a federal or state legislative enactment; it may be a single act of a legislature or a body of acts which are collected and arranged for a session of a legislature (see statutory law).

Statutory law—laws promulgated by Congress and state legislatures.

Waiver of consent—the Common Rule allows investigators to conduct research without subject consent under certain circumstances; for a waiver of consent requirements pursuant to 45 CFR 46.116(d), the IRB must find and document that (1) the research involves no more than minimal risk to the subjects; (2) the waiver will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.