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Federal Protection for Human Research Subjects: An Analysis of the Common Rule and Its Interactions with FDA Regulations and the HIPAA Privacy Rule

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Summary

The Common Rule (45 CFR 46, Subpart A) governs research that is conducted on human beings if it is funded by one of 18 federal agencies. It requires a review of proposed research by an Institutional Review Board (IRB), the informed consent of research subjects, and institutional assurances of compliance with the regulations.

In 1974, 45 CFR 46 was published following some cases of harm to human subjects, such as those caused by thalidomide drug trials and the United States Public Health Service syphilis study in Tuskeegee, Alabama. The regulations had their roots in numerous international agreements, such as the Nuremberg Code and the Declaration of Helsinki, and domestic policies, such as those put forth by the Department of Health, Education and Welfare (DHEW; now the Department of Health and Human Services, HHS). In 1991, 16 federal agencies adopted 45 CFR 46, Subpart A, which then became known as the Common Rule.

Since the Common Rule took effect, events like the death of Jesse Gelsinger in 1999 due to his participation a clinical trial have prompted scrutiny of the Rule and its ability to protect research subjects. In order to help enhance research subject protections, in 2000 HHS removed the Office for Protection from Research Risks (OPRR) from the National Institutes of Health (NIH), and created a new office — the Office for Human Research Protections (OHRP) — in an elevated position in HHS. In addition, groups like the National Bioethics Advisory Commission and the National Academies raised the following policy questions: (1) Should the Common Rule be applied to non-federally funded research, social and behavioral research, international clinical trials, and research with human biological materials? (2) Do existing provisions ensure the participation and protection of children, prisoners, minorities, those with diminished capacity, pregnant women, fetuses, neonates, and people in emergency situations? (3) What should be the requirements regarding IRBs' membership, responsibilities, training, and registration? (4) How should conflicts of interest, accreditation, ongoing research, and adverse event reporting be handled? (5) How should basic and research-related medical care's cost, and IRB liability for harm be handled? (6) How should the human subjects protection system be reassessed, adequate resources ensured, and the burdens and benefits of amending regulations appropriately weighed? (7) How does 45 CFR 46 interact with the Food and Drug Administration (FDA) regulations for the protection of human subjects (21 CFR 50 and 56), and the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (45 CFR 146)?

Legislation to revise the Common Rule has been introduced in every Congress since 1997. In the 109th, the PhRMA Act of 2005 (H.R. 870) was introduced, to provide criminal penalties for concealing evidence of serious drug adverse events. Bills introduced in former Congresses include the Protection for Participants in Research Act of 2003 (H.R. 3594, 108th Congress), the Research Revitalization Act of 2002 (S. 3060, 107th Congress), and the Human Research Subject Protections Act of 2002 (H.R. 4697, 107th Congress). This report will be updated as needed.

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Introduction

Congress has shown a keen interest in the Common Rule largely because of the federal government's longstanding investment in medical research, and its interest in research-subject safety. The Common Rule (45 CFR 46, Subpart A) is a set of regulations that govern most federally funded research conducted on human beings. Its three basic requirements are aimed at protecting research subjects: the informed consent of research subjects, a review of proposed research by an Institutional Review Board (IRB), and institutional assurances of compliance with the regulations.

Informed Consent. Meaningful informed consent is one cornerstone of human subjects protections. To provide informed consent, a potential research subject must both understand what participation in a study entails (in other words, be informed), and agree to participate (consent). The Common Rule requires that a researcher obtain informed consent (usually in writing) from a living person or their legally authorized representative before the person can be admitted to a study.

The Common Rule's informed consent regulations focus primarily on the elements and documentation of informed consent rather than on the process used to obtain it. As to the process, the regulations require that informed consent be sought only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. Regarding the content and documentation, the Common Rule requires that information be given in language understandable to the subject, and that informed consent be clear of any exculpatory language releasing the investigator, the sponsor, the institution or its agents from liability for negligence (45 CFR 46.116). In addition, the Common Rule specifies that all of the following elements must be provided when informed consent is sought (45 CFR 46.116(a)):

- a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- a description of any reasonably foreseeable risks or discomforts to the subject;
- a description of any benefits to the subject or to others which may reasonably be expected from the research;

- a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
- an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
- a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When informed consent is sought, the Common Rule also requires other information to be provided if applicable, such as any additional costs to the subject that may result from participation in the research, or a statement that the particular treatment or procedure may involve risks to the subject, which are currently unforeseeable (45 CFR 46.116(b)).

IRB Review. The Common Rule's primary mechanism for ensuring the adequacy of informed consent and other aspects of human subjects protection is IRB review. IRBs review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by the Common Rule (45 CFR 46.109(a)). The Common Rule requires that protocols for human subjects research be IRB approved before the research can begin (45 CFR 46.103(b)). The Common Rule does not require that IRBs be accredited,[1] but it does require them to meet certain membership and review procedures.

IRBs generally comprise volunteers who examine proposed and ongoing scientific research to ensure that human subjects are properly protected. The Common Rule (45 CFR 46.107) requires that each IRB have the following:

- at least five members;
- members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution;
- members that are not entirely of one profession;
- at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas;
- at least one member who is not affiliated with the institution;

[1] Accreditation is procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks.

- a membership diverse in race, gender, and cultural backgrounds, and having sensitivity to community attitudes; and
- if an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

IRBs are to meet as necessary (in institutions with a high volume of protocols, this is often monthly or more frequently; in smaller-volume institutions it is often less frequently), to conduct their reviews. Reviews may be conducted only at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it must receive the approval of a majority of those members present at the meeting (45 CFR 46.108(b)). IRBs are to conduct initial reviews of proposed research, and also monitor ongoing research, re-reviewing it at least once per year (45 CFR 46.109(e)). No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB (45 CFR 46.107(e)). To facilitate this monitoring and reevaluation, IRBs are to be provided with reports of unanticipated problems involving risks to subjects (or others) that arise during research,[2] and to reevaluate the human subjects protections in the protocol if necessary (45 CFR 46.103(b)(5)).

The Common Rule does not specify which procedures an IRB must follow in its review of protocols — leaving that to local control — but it does require that there be written procedures. The procedures must specify how an IRB will conduct its initial and continuing reviews of research, report its findings and actions to the investigator and the institution, and determine which projects require review more often than annually and which need verification from sources other than the investigators that no material changes have occurred since previous IRB review. In addition, there must be written procedures that ensure prompt reporting to the IRB of unanticipated problems, noncompliance, and proposed changes in research activities (45 CFR 46.103(b)(4)-(5)).

The Common Rule requires that an IRB determine that all of the following requirements are satisfied in order to approve proposed research (45 CFR 46.111):

- informed consent is sought from each subject according to the requirements described above;
- risks to subjects are minimized;
- risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result;
- that the selection of subjects is equitable;

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[2] Some unanticipated problems involving risks to subjects may be referred to as *adverse events* (AEs), although the term is not used in the Common Rule itself.

- when appropriate, that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- when appropriate, that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and
- if some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, that the study has additional safeguards to protect the rights and welfare of these subjects.

In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility (45 CFR 46.111(a)(2). The Common Rule leaves the weighing of risks and benefits in individual protocols up to local IRBs, enabling them to apply local community standards.

Not every research project involving human subjects is required to gain IRB approval through the formal review process described above. Certain types of research projects may qualify for *expedited review*. Expedited review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure. The Common Rule allows an IRB to use an expedited review procedure for one or both of the following: (1) research that the HHS Secretary has determined to be eligible for expedited review[3] and found by the reviewer(s) to involve no more than *minimal risk*; (2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

The Common Rule defines *minimal risk* as that in which 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 (45 CFR 46.102(i)).

Assurance of Compliance. The Common Rule's primary mechanism for ensuring that a research institution is complying with regulatory requirements for IRBs and for other human research subject protections is through requiring institutional *assurances*. An assurance is a written document containing promises of regulatory compliance. To receive federal funding for research covered by the Common Rule, each institution is required to provide an assurance of compliance

[3] A list of the HHS Secretary's categories of research that qualify for expedited review is available at [http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm], visited Apr. 14, 2005.

with the Common Rule to the head of the federal Department or Agency from which it is receiving funding. As an alternative, the institution may substitute an assurance provided to Office for Protection from Research Risks (OPRR, now the Office for Human Research Protections: OHRP), if the assurance is current, approved for federal-wide use by HHS, and applicable to the research in question. (45 CFR 46.103(a))

To satisfy the Common Rule's requirements, an assurance must certify that the research has been reviewed, approved, and will be subject to continuing review by an IRB (45 CFR 46.103(b)). The assurance must include, among other things:

- designation of one or more IRBs established in accordance with the requirements of the Rule, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties(45 CFR 46.103(b)(2)).
- written IRB procedures for initial, continuing, and expedited review, and for ensuring prompt reporting of certain unanticipated problems (45 CFR 46.103(b)(4)-(5)).
- a statement of principles governing the institution for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation (45 CFR 46.103(b)(1).
- a list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant (45 CFR 46.103(b)(2)).

Through the assurance process, the HHS Office for Human Research Protections — which can approve assurances for federal-wide use — may gather the above information about some IRBs.

The Common Rule and 45 CFR 46. The Department of Health and Human Services (HHS) (formerly the Department of Health Education and Welfare — DHEW - until 1980) was the first federal agency to publically develop formal policies for the protection of human subjects.[4] In 1974, after more than 20 years of DHEW involvement and consideration, the regulations were codified: 45 CFR 46, Subpart A. In 1991, Subpart A of 45 CFR 46 was adopted by 16 federal agencies, and thus became known as the Common Rule.

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[4] In 1953, Secretary of Defense Charles Wilson issued a top secret memorandum establishing policy for research related to atomic, biological, and chemical warfare. The policy incorporated the principles of the Nuremberg Code and two additional protections — a prohibition on research involving prisoners of war and a requirement that the Secretary of the appropriate military service approve research studies. National Bioethics Advisory Commission, *Ethical and Policy Issues in Research Involving Human Participants*, Aug. 2001, p.151.

Since 1974, HHS has promulgated and amended additional regulations to give extra protections to certain groups of human subjects, including children, prisoners, and pregnant women, as well as fetuses and human in vitro fertilization. These regulations for the protection of vulnerable populations. 45 CFR 46 Subparts B, C, and D provide protections for women and neonates, prisoners, and children, respectively. These Subparts apply to HHS funded research, but are not a part of the Common Rule. They do not generally apply to the other federal agencies that have adopted the Common Rule, except for cases in which an agency has voluntarily adopted one or more of the additional Subparts. In this report, 45 CFR 46 will refer to the full regulation, including all Subparts. The Common Rule will refer only to 45 CFR 46, Subpart A.

Today the Common Rule governs 18 federal departments and agencies.[5] The Common Rule applies to research conducted at or funded by the agencies that have adopted it, though it has not been adopted by all agencies that fund research.[6] This means that, in order to be eligible to receive funding from one of the agencies that has adopted the Common Rule and/or other subsections of 45 CFR 46, researchers and institutions must abide by the relevant regulatory provisions.[7] It also means that federal law does not require research conducted without federal money (or with money from an agency that has not adopted the Common Rule and/or other Subparts of 45 CFR 46) to be conducted in accordance with these regulations. A number of private companies have voluntarily chosen to follow the Common Rule, though these are not subject to federal enforcement mechanisms if they fail to comply.

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[5] The Common Rule was developed as such by the Interagency Federal Coordinating Council for Science, Engineering and Technology. The following departments and agencies have adopted it: Department of Health and Human Services, Department of Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of Defense, Consumer Product Safety Commission, International Development Cooperation Agency (Agency for International Development), Department of Housing and Urban Development, Department of Justice, Department of Defense, Department of Education, Department of Veterans Affairs, Environmental Protection Agency, National Science Foundation, and Department of Transportation. The Rule applies to the Central Intelligence Agency (by Executive Order 12333), and the Social Security Administration (by P.L. 103-296). The Office of Science and Technology Policy signed but did not codify the Rule because it does not conduct clinical research.

[6] For example, the Department of Labor and the Nuclear Regulatory Commission are reported to sponsor human subjects research but have not adopted the Common Rule. The Department of Homeland Security (DHS) has not adopted the Common Rule. *House Report 107-609 of the Homeland Security Act of 2002* specifies that civilian human health-related research and development activities relating to countermeasures for chemical, biological, radiological, and nuclear and other emerging terrorist threats are to be carried out by HHS in collaboration with DHS, rather than by DHS itself. HHS follows not only the Common Rule, but all Subparts of 45 CFR 46.

[7] The Common Rule exempts some categories of research from its requirements, and gives Department or Agency heads final judgment as to whether a particular activity is covered. Examples of types of research that may qualify as exempt are those that involve the use of educational tests, demonstration projects conduced by Agency heads to assess public benefit or service programs, and some others (45 CFR 46.101(b), (c)).

Some federal agencies and departments have adopted Subparts of 45 CFR 46 other than the Common Rule, or have implemented their own regulations governing certain types of human subjects research. For example, the Department of Education has adopted Subpart D, which provides additional protections for children involved in research (35 CFR 97.401-409). The Department of Justice's Bureau of Prisons has adopted its own regulations regarding research involving prisoners, which are similar to, though more rigorous than 45 CFR 46, Subpart C (28 CFR 512.10-21). The Department of Veterans Affairs has an Office of Research Oversight, which is responsible for advising the Under Secretary for Health on matters of compliance and assurance in human subjects protections, research safety, and research impropriety and misconduct (P.L. 108-170, § 401). In addition, the Veterans Administration has engaged an external contractor to inspect and certify the human subjects protection program of every VA facility conducting research involving human subjects.[8]

Other Federal Regulations. The Common Rule and other parts of Subparts of 45 CFR 46 are not the only federal regulations that may provide protections for human subjects. One additional set of federal regulations for the protection of human subjects has been put forth by the Food and Drug Administration (FDA). FDA is the federal agency responsible for reviewing the safety and efficacy of new biomedical products (drugs, devices, vaccines, etc.) before they can be marketed in the United States. FDA's regulations for the protection of human subjects (21 CFR 50, 56) are very similar to — and in many instances identical to — the Common Rule. They require informed consent (21 CFR 50), IRB review (21 CFR 56), and assurance of IRB review (21 CFR 312.66).

There are some key differences between FDA regulations, and the Common Rule and other Subparts of 45 CFR 46. FDA regulations have a scope and set of definitions targeted to clinical trials[9] that evaluate products for marketing rather than to basic research.[10] The broadest difference is that, unlike the Common Rule, FDA's regulations for the protection of human research participants attach when research is

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[8] Testimony of Thomas L. Garthwaite, M.D., Under Secretary for Health, Department of Veterans Affairs on the *Protection of Human Subjects of Research in the Veterans Health Administration* before the Subcommittee on Oversight and Investigations of the Committee on Veterans' Affairs, U.S. House of Representatives (Sept. 28, 2000), at [http://veterans.house.gov/hearings/schedule106/sept00/9-28-00/tgarthwa.htm], visited May 3, 2005.

[9] A clinical trial is one type of human subjects research in which a hypothesis is tested in a randomized, controlled and usually blinded setting. "Randomized" means that the subjects have been randomly divided into two or more groups; one or more group(s) receive an intervention (such as a drug) and another (a control group) does not. "Controlled" means steps have been taken to minimize the effects of variables other than the intervention that might affect the outcome (such as, for example, subjects' age, health problems, etc.). "Blinded" means that the subjects, and sometimes the researchers interacting with the subjects and recording results, do not know which group the subjects are in. Human-subjects research is a broader category than clinical trials, which would include non-clinical trials such as surveys and observational studies.

[10] Basic research is broadly defined as asking questions to obtain knowledge. It may encompass laboratory, animal, or other study methods. It is a broader category than human subjects research (which is basic research that involves human beings).

used to support an application to FDA for marketing, regardless of the funding source. Other subtler distinctions, which have prompted public calls for harmonizing the two sets of regulations include FDA's regulatory provisions for emergency use of a product in a critical situation, and requirements for investigators to disclose financial conflicts of interest, whereas the Common Rule does not. In addition, 45 CFR 46 makes two allowances that FDA regulations do not: for international research, 45 CFR 46, Subpart A (the Common Rule), allows a department or agency head to approve the substitution of foreign procedures in lieu of HHS policy; and for research involving children, 45 CFR 46, Subpart D, stipulates that an IRB may waive the parental consent requirement if necessary to protect the subjects.

A third set of federal regulations that may provide some protections for human subjects is the *Standards for Privacy of Individually Identifiable Health Information,*[11] or *Privacy Rule* (45 CFR 164), which the HHS Secretary issued pursuant to the *Health Insurance Portability and Accountability Act of 1996*. (HIPAA, P.L.104-191) HIPAA's stated purpose focused broadly upon health insurance — improving portability and continuity of health insurance coverage, to combating waste, fraud, and abuse in health insurance and health care delivery, to simplifying the administration of health insurance, among other things. The Privacy Rule regulates certain health-related entities' (*covered entities*')[12] handling of *protected health information* (PHI - which is, generally speaking, individually identifiable health information). When human subjects research involves the handling of PHI by a covered entity, the protections of the Privacy Rule attach, regardless of the funding source, or whether the research will be used to support an application to FDA for marketing.

The requirements of the Privacy Rule are somewhat different than those of the Common Rule. Whereas the Common Rule requires informed consent before the person can participate in research, the Privacy Rule requires a patient's *authorization* for the release of his or her PHI (45 CFR 46.508).[13] The elements of authorization are focused on disclosure of information rather than on preparation for participation in research. Elements include, for example, that authorization must be in plain language, contain a description of the information and its proposed use(s), contain the name of the person requesting authorization, list a start and end date for the

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[11] For more information, see CRS Report RS20500, *Medical Records Privacy: Questions and Answers on the HIPAA Final Rule,* by C. Steven Redhead.

[12] A *covered entity* is a health plan, health clearing house, or any health care provider who transmits health information in electronic form in connection with transactions for which the HHS Secretary has adopted standards under HIPAA (45 CFR 164.103).

[13] The Privacy Rule specifically permits authorization to be combined with informed consent (45 CFR 164.508(b)(3)(i)). In addition, in some circumstances — including the conduct of research — the Privacy Rule's requirements may be satisfied by either informed consent or authorization. See, e.g., 45 CFR 164.532(a). There are also certain exceptions to the authorization requirement, which allow for standard health-provider and insurer business practices, for the provision of health care, and for circumstances in which the requirement has been waived by an IRB or privacy board (45 CFR 504-506).

research, include the authorization's expiration date, and state the individual's right to revoke his or her authorization.[14]

The Privacy Rule requires authorization for the release of PHI, in some cases in which the Common Rule does not require informed consent, for example, for post-mortem research (the Common Rule applies only to research involving living persons).[15] One other distinction is that, although the Privacy Rule allows authorization to be combined with informed consent, it specifically prohibits the combination of authorizations for various research projects (*compound authorization*) (45 CFR 164.508(b)(3)). The Common Rule contains no equivalent prohibition. Another distinction is that the Privacy Rule does not require oversight for background research[16] that is conducted without removing PHI from the covered entity (45 CFR 164.512(i)(1)(ii)). Under the terms of the Common Rule, this type of inquiry would constitute human subjects research and trigger regulatory provisions (45 CFR 46.102(d)).

Another point of distinction between the Privacy Rule and the Common Rule is that the Privacy Rule allows for certain actions to be taken by either an IRB or a *privacy board*. The Common Rule requires action by an IRB. According to the terms of the Privacy Rule, a privacy board, which may be an IRB (45 CFR 164.512(i)(1)(i)(B)):

- has members with varying backgrounds and appropriate professional competency as necessary to review the effect of the research protocol on the individual's privacy rights and related interests;
- includes at least one member who is not affiliated with the covered entity, not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities; and
- does not have any member participating in a review of any project in which the member has a conflict of interest.

Because the Common Rule, 45 CFR 46, FDA regulations, and the Privacy Rule all have different triggers, human subjects research may have to meet all, some, or none of these federal requirements. For example, an HHS-funded study conducted by a hospital to help test a drug for marketing would be subject to all of the regulations. A privately-funded study conducted in a practitioner's office to compare surgical techniques may be subject to none of them.

Concerns About the Common Rule. Though the spectrum of regulations that may govern human subjects research have been implemented over time, the

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[14] For a full list of the required elements of authorization, see 45 CFR 164.508 (c).

[15] 45 CFR 164.502(f) (Privacy Rule); 45 CFR 46.102(f) (Common Rule). There are certain exceptions to the Privacy Rule's requirement regarding postmortem research at 45 CFR 164.512(i)(1)(iii).

[16] Background research might entail reviewing patients' medical files to determine the frequency of a common intervention, so that the need for an improved intervention could be evaluated.

regulations that are the basis of the Common Rule were crafted over 30 years ago. At that time, a research project was typically conducted at a single location, and was largely federally funded. Since the original regulations took effect, the number of privately funded and/or multi-center trials has increased. Events such as the 1999 death of Jesse Gelsinger due to his participation in a clinical trial have led some policy makers to call for changes to the Common Rule.

Concerns about the Common Rule have been expressed in a number of areas:

- The Rule does not apply to all federally funded or any non-federally funded human subjects research; therefore, some research may be conducted without federal oversight and without protection for human subjects.
- Vulnerable populations may not receive adequate protection in research because Subparts B-D of 45 CFR 46, which are designed to protect children, prisoners, pregnant women, human fetuses, and neonates, have not been uniformly adopted by agencies other than HHS; in addition, the Common Rule does not contain provisions specific to research on minority populations, or to research on those with diminished capacity in emergency situations.
- Some IRBs may have duties too broad and memberships too narrow to ensure proper protections. In addition, variance in different IRBs' reviews may lead investigators to seek more lenient IRBs, a process sometimes called "IRB shopping."
- Rules governing conflicts of interest, accreditation of investigators, sponsors, and IRBs, adverse event reporting, and monitoring of ongoing research may need more refinement to function optimally.
- Who should pay for routine and injury-related medical care during research remains unresolved.
- Mechanisms to easily refine the Common Rule are not in place.
- Simultaneous application of the Common Rule, the Privacy Rule, and/or FDA regulations have created confusing requirements for some conducting human subjects research.

The related topic of the reporting and publication of clinical trials data and results is beyond the scope of this report and is not discussed herein.[17]

HHS has the authority to address some of the above issues by amending the Common Rule, though it does not have the authority to apply the Common Rule or other parts of 45 CFR 46 to research conducted without federal funding. In addition, HHS does not have the authority to regulate its sister agencies, so each agency that has adopted Common Rule (and each company that now voluntarily follows the Rule) would have to make an independent decision to adopt and implement

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[17] For additional information regarding clinical trials reporting and publication, see CRS Report RL32832, *Clinical Trials Reporting and Publication*, by Erin D. Williams.

amendments made by HHS. Therefore, groups such as the National Bioethics Advisory Commission[18] and the National Academies[19] have called on Congress to address issues related to the human subject protection through legislation.

Proposed Legislation. Several bills have been introduced on topics related to the Common Rule. In the 109th Congress, Representative Pete Stark introduced legislation on a topic related to the Common Rule: reporting of adverse events related to drugs submitted for FDA approval or approved by FDA. The bill, H.R. 870 (the PhRMA Act of 2005) would create criminal penalties, including fines and imprisonment, for drug manufacturers' executives who knowingly conceal reports of serious adverse drug experience.

In the 108th Congress, Representative Diana DeGette introduced H.R.3594, the Protection for Participants in Research Act of 2003. This bill would have extended the scope of the Common Rule and other Subparts of 45 CFR 46 to all public as well as private research, and would have required the HHS Secretary to harmonize the Rule with FDA's regulations. In the 107th Congress, Senator Edward Kennedy introduced S. 3060, the Research Revitalization Act of 2002, and Representative DeGette introduced H.R. 4697, the Human Research Subject Protections Act of 2002, which was similar to H.R.3594 (108th Congress). S. 3060 would have created national standards for protecting human subjects in research that would have been overseen by a new HHS office: the National Office of Human Research Protections. The standards would have applied all of 45 CFR 46 to all research conducted in the United States, funded by the United States government, or subject to United States regulatory review. In addition, the bill would have required accreditation of IRBs, voluntary cooperative IRB review for multi-site research, identification of countries with human subject protections that were substantially equivalent to the United States for studies conducted overseas, and disclosure of financial conflicts of interest by investigators and IRB members. Finally, S. 3060 would have made enforcement action possible in district court against investigators, sponsors, or the IRB for failure to comply with the regulations.

Report Contents. This report contains several sections, assembled to provide a comprehensive overview of the Common Rule. The first section explores the history of the Rule, focusing on issues and foreign and domestic policies that led to its creation. The second section explores the current issues, studies and proposals that have been made with respect to the Rule. Topics include the Rule's scope, its treatment of vulnerable populations, its governance of IRBs, its mechanisms for addressing mistakes and misconduct, human subjects' access to medical care, and mechanisms for ongoing research on the Rule. **Appendix A** explores the interaction of the Privacy Rule and FDA regulations with the Common Rule. **Appendix B**

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[18] In 1995, President Clinton established the National Bioethics Advisory Commission (NBAC) by Executive Order, to identify broad principles to govern the ethical conduct of research, among other things. NBAC's charter expired in 2001.

[19] The National Academies is an organization comprising four non-profit institutions (the National Research Council, the National Academy of Sciences, National Academy of Engineering, and Institute of Medicine) that provide science, technology and health policy advice under a congressional charter. See [http://www.nationalacademies.org], visited Apr. 11, 2005.

contains a detailed history of the evolution of human subjects protections leading up to the Common Rule.

History of the Common Rule and Current Regulations

Research conducted on human beings is governed by a series of international codes, national legislation, and agency regulations. The regulatory framework has evolved over time, often shifting in the aftermath of tragedy. The following is a timeline of seminal events that led to the creation of the Common Rule. A more detailed historical overview is contained in **Appendix B: History and Requirements of the Common Rule**.

Prior to 1940s:

- Physicians self-regulate their research using the *Hippocratic Oath*.

1940s:

- The *Nuremberg Code* is created by the international community after the Holocaust, for the first time requiring individual research subjects' informed consent. The Code was not specifically adopted into US law, but later became the basis of the Common Rule.

1953:

- The United States' National Institutes of Health (NIH) opens its Clinical Center, and the DHEW Secretary issues *Group Consideration of Clinical Research Procedures Deviating from Accepted Medical Practice or Involving Unusual Hazard*, requiring peer review of intramural human subjects research. Research funded by NIH was not covered by this rule unless it was conducted there.
- The Secretary of Defense, Charles Wilson, issued a Top Secret memorandum establishing policy for research related to atomic, biological, and chemical warfare. The policy incorporated the principles of the Nuremberg Code and two additional protections — a prohibition on research involving prisoners of war and a requirement that the Secretary of the appropriate military service approve research studies.

1962:

- Thalidomide, a drug provided experimentally to pregnant women in the United States, is linked to the birth defect phocomelia.[20]
- Congress enacts the *Drug Amendments of 1962* (P.L. 87-781), requiring researchers to obtain subjects' informed consent before

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[20] Phocomelia Syndrome is a birth defect that may occur sporadically, or occasionally may be inherited. In some cases it may be caused by exposure to toxins, such as certain drugs (e.g., thalidomide) taken by a pregnant woman. It is characterized by missing or deformed arms and/or legs. Other symptoms may include growth and mental deficiencies, and defects in the eyes, ears, and nose. For further information, see [http://my.webmd.com/hw/health_guide_atoz/nord780.asp].

conducting research on them, and requiring Food and Drug Administration (FDA) to review the safety and efficacy of new drugs before they are sold in the United States.
- A federally funded study of United States medical schools concludes that internal institutional regulation of human subjects research is erratic.

1964:
- The World Medical Association, an international group of physicians, creates the *Declaration of Helsinki*, to help engender public trust in biomedical research. The Declaration is a statement of ethical principles to provide guidance to investigators and participants in human subjects research.
- NIH's research resource division warns the Director of "possible repercussions" due to the absence of an applicable code of conduct for research, among other things.

1966:
- Researcher Henry Beecher publishes 22 detailed cases of studies that contained serious or potentially serious ethical violations, some resulting in the preventable deaths of patients.
- The United States Surgeon General publishes the policy *Clinical Investigations Using Human Subjects*, requiring prior committee review for all Public Health Service-funded human subjects research, expanding the regulations to cover extramural research.
- The responsibility for education and enforcement of the Surgeon General's policy falls to the Institutional Relations Branch of the Division of Research Grants for the National Institutes of Health (IRB/DRG/NIH).

1971:
- DHEW provides guidance about how to apply the Surgeon General's 1966 policy, in *Institutional Guide to DHEW Policy on Protection of Human Subjects*, listing the elements of informed consent, and requiring continual review of ongoing research projects.

1972:
- The public learns about the United States Public Health Service-funded *Tuskeegee syphilis study*, in which researchers withheld treatment from affected African-American men for 40 years, 19 years past the discovery of penicillin, which can cure the disease.
- A DHEW ad-hoc advisory panel to review Tuskeegee finds that the study was ethically unjustified, and recommends that Congress create a permanent body with authority to regulate all federally supported and conducted human subjects research.
- The NIH Director creates the Office for Protection from Research Risks (OPRR) from the IRB/DRG/NIH and locates it in his office.

1974:

- DHEW replaces its 1966 policy and 1971 guidance with comprehensive regulations governing the protection of human subjects, forming Subpart A of 45 CFR 46.
- Congress passes the *National Research Act* (P.L. 93-348), which creates the *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research* (the National Commission) and directs it to make recommendations to the DHEW Secretary about the ethical principles that should underlie human subjects research. The Act also requires grantees and contractees under the Public Health Service Act to establish IRBs to review research involving human subjects.

1975:

- The DHEW Secretary publishes regulations with additional protections for research involving fetuses, pregnant women, and human in vitro fertilization (40 Federal Register 33526), forming the initial version of Subpart B of 45 CFR 46.[21]

1978:

- The DHEW Secretary publishes regulations with additional protections for prisoners who are subjects in to biomedical and behavioral research (45 Federal Register 53655), forming the initial and current version of Subpart C of 45 CFR 46.
- The DHEW Secretary publishes proposed regulations for research involving those who are institutionalized as mentally disabled. (43 Federal Register 53950) These proposed regulations were not adopted.

1979:

- The National Commission publishes the *Belmont Report*, articulating three ethical principles of biomedical research: (1) respect for persons, (2) beneficence, and (3) justice.

1980:

- FDA publishes regulations that govern the protection of human subjects in trials conducted to support an application to market a product (45 Federal Register 36390). The regulations form 21 CFR 50.
- DHEW officially becomes HHS.

1981:

- In response to the *Belmont Report*, HHS revises its human subjects regulations (45 CFR 46, Subpart A).

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[21] Subsequent changes were incorporated January 11, 1978 (43 FR 1758), November 3, 1978 (43 FR 51559), June 1, 1994 (59 FR 28276), and November 13, 2001 (66FR 56775). Only the most recent 2001 revision is listed in the timeline above.

- FDA published regulations that govern the operations and functions of IRBs in reviewing trials conducted to support an application to market a product. (46 Federal Register 8975) The regulations form 21 CFR 56.

1983:

- The *President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research* issues *Implementing Human Research Regulations: The Adequacy and Uniformity of Federal Rules and of Their Implementation* (the Commission Report), analyzing the rules and procedures of the Federal entities conducting or supporting human subjects research. It concludes that 45 CFR 46 (Subpart A) is the benchmark policy for the agencies.
- The HHS Secretary publishes regulations with additional protections for children involved as research subjects (48 Federal Register 9818), forming the initial version of Subpart D of 45 CFR 46.

1991:

- In response to the Commission Report, Subpart A of 45 CFR 46 (basic HHS Policy for Protection of Human Research Subjects) is adopted by 16 federal agencies, and at that point becomes known as the *Common Rule*.
- The HHS Secretary updates protections for children involved as research subjects (56 Federal Register 28032), forming the current version of Subpart D of 45 CFR 46.

1994:

- President Clinton issues a memorandum on February 17 (*Memorandum for the Vice President, the Heads of Departments of Executive Agencies, Subject: Review of Federal Policy for the Protection of Human Subjects*), directing each department and agency of Government to review present practices to assure compliance with the Federal Policy for the Protection of Human Subjects and to cease immediately sponsoring or conducting any experiments involving humans that do not fully comply with the Federal Policy.

1996:

- Congress passes the Health Insurance Portability and Accountability Act of 1996 (HIPAA) that includes a requirement that the HHS Secretary establish rules to protect the privacy of consumers' health information.

2000:

- The HHS Secretary issues the *Privacy Rule* pursuant to HIPAA, establishing a set of basic consumer protections for certain health-related entities' uses and disclosures of consumers' protected health information.

- HHS replaces OPRR with the Office for Human Research Protections (OHRP) and elevates the office from NIH to HHS.

2001:

- The HHS Secretary updates Subpart B of 45 CFR 46 (66 Federal Register 56775-56780) to the version currently in force, continuing the special protections for pregnant women and human fetuses and making limited changes in terminology referring to neonates, clarifying provisions for paternal consent when research is conducted involving fetuses, clarifying language that applies to research on newborns of uncertain viability, and correcting technical errors.

2002:

- The HHS Secretary amends the Privacy Rule, adding the requirement that health care providers make a good faith effort to obtain a written acknowledgment of receipt of the provider's privacy notice from those whom they treat directly.

Issues, Recommendations, and Proposed Legislation

The conduct of research has been transformed by many factors since 45 CFR 46 was first adopted in 1974. Key changes include the growth in both federally and industry-sponsored biomedical research, which has resulted in a much larger and more complex enterprise. To address the issues raised by the shifting research landscape, a number of key reports have been published. (See **Table 1** for a list of key reports). The reports have raised issues and made recommendations in a number of areas. Broadly, the issue areas include the scope of the Common Rule, treatment of vulnerable populations, IRB issues, preventing mistakes and misconduct, addressing injuries and medical care, and handling the future of human subjects protections. The sections that follow provide an overview of the dilemmas defined and recommendations made in the key reports.

Table 1. Key Human Subjects Protection Reports, 1995-2004

1995: — Advisory Committee on Human Radiation Experiments Report (Advisory Committee on Human Radiation Experiments) at [http://www.eh.doe.gov/ohre/roadmap/achre/report.html]
1996: — Scientific Research: Continued Vigilance Critical to Protecting Human Subjects (General Accounting Office - GAO) at [http://www.gao.gov/archive/1996/he96102t.pdf]
1998: — Institutional Review Boards: Their Role in Reviewing Approved Research (HHS Office of the Inspector General - OIG) at [http://oig.hhs.gov/oei/reports/oei-01-97-00190.pdf] — Institutional Review Boards: Promising Approaches (OIG) at [http://oig.hhs.gov/oei/reports/oei-01-97-00191.pdf] — Institutional Review Boards: The Emergence of Independent Boards (OIG) at [http://oig.hhs.gov/oei/reports/oei-01-97-00192.pdf] — Institutional Review Boards: A Time for Reform (OIG) at [http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf] — Final Report on Low-Volume Institutional Review Boards (OIG) at [http://oig.hhs.gov/oei/reports/oei-01-97-00194.pdf] — Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity (National Bioethics Advisory Commission - NBAC) at [http://www.georgetown.edu/research/nrcbl/nbac/capacity/TOC.htm]
1999: — Research Involving Human Biological Materials: Ethical Issues and Policy Guidance (NBAC) at [http://www.bioethics.gov/reports/past_commissions/nbac_biological1.pdf]
2000: — Protecting Human Research Subjects: Status of Recommendations (OIG) at [http://oig.hhs.gov/oei/reports/oei-01-97-00197.pdf] — Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research (OIG) at [http://oig.hhs.gov/oei/reports/oei-01-97-00195.pdf] — Recruiting Human Subjects: Sample Guidelines for Practice (OIG) at [http://oig.hhs.gov/oei/reports/oei-01-97-00196.pdf]
2001: — Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (NBAC) at [http://www.bioethics.gov/reports/past_commissions/nbac_international.pdf] — Ethical and Policy Issues in Research Involving Human Participants (Aug. 2001; NBAC), at [http://www.bioethics.gov/reports/past_commissions/nbac_human_part.pdf] — Preserving Public Trust: Accreditation and Human Research Participant Protection Programs (Institute of Medicine - IOM - Committee) at [http://books.nap.edu/catalog/10085.html]
2002: — Clinical Trial Websites: A Promising Tool to Foster Informed Consent (OIG) at [http://oig.hhs.gov/oei/reports/oei-01-97-00198.pdf] — Responsible Research: A Systems Approach to Protecting Participants (IOM Committee) at [http://www.iom.edu/report.asp?id=4459]
2002-2003: — Transcripts on research ethics (President's Council on Bioethics - PCBE) at [http://www.bioethics.gov/topics/experiment_index.html]
2003: — Protecting Participants and Facilitating Social and Behavioral Sciences Research (National Research Council - NRC Panel) at [http://www.nap.edu/catalog/10638.html] — The Ethical Conduct of Clinical Research Involving Children (IOM Committee) at [http://www.iom.edu/report.asp?id=19422]
2004: — Intentional Human Dosing Studies for EPA Regulatory Purpose (NRC, National Academy of Sciences - NAS) at [http://books.nap.edu/catalog/10927.html] — The Ethical Conduct of Clinical Research Involving Children (IOM Committee) at [http://www.iom.edu/report.asp?id=19422]

Scope of the Common Rule

The protections and restrictions afforded by the Common Rule do not apply to all research. Questions have been raised regarding which research should be governed by the Common Rule, and the effect that the rule has on some specific types of research.

Non-Federally Funded Research and Federally Funded Research Outside the Scope of the Common Rule. The Common Rule governs only research funded by agencies that have adopted 45 CFR 46, Subpart A. This limitation may be important, as it has been reported that industry, rather than the federal government, provides an estimated seventy percent of the funding for clinical drug trials conducted in the United States.[22] Other federal regulations that may apply to human subjects research are also limited in their application. FDA requirements only extend protections to clinical trials that support applications to market a medical product, or other areas over which FDA has jurisdiction, regardless of funding source. The HIPPA Privacy Rule's protections only regulate the flow of personally identifiable information, and extend only to non-background research conducted by covered entities, such as hospitals or medical clearing houses. Because of these limitations, some clinical research (for example, a doctor's non-federally funded study to compare methods of plastic surgery)[23] falls outside the scope of HHS, FDA, and HIPAA regulations, and therefore is not subject to federal informed consent and IRB review requirements.[24] Information is not generally collected about human subjects studies that fall outside the scope of federal regulations, so the precise number of these studies is not known; however, a few sensational cases have been reported in the media.[25]

Companies and other organizations may voluntarily choose to apply the Common Rule and/or other Subparts of 45 CFR 46 to their research projects. However research projects in which compliance is voluntary are not subject to oversight or disciplinary action by the HHS. In *Responsible Research: A Systems*

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[22] See, e.g., Michelle Mello, et al., "Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry," *The New England Journal of Medicine*, vol. 351, no. 21, p. 2202 (May 26, 2005).

[23] P.J. Hilts, "Study or Human Experimentation? Face-Lift Project Stirs Ethical Concerns." *New York Times*, June 21, 1998, p. A-25.

[24] Health care institutions and universities generally have their own IRBs and requirements for IRB review of research, which may exceed federal requirements. However, an infraction of institutional policies does not itself constitute a breach of federal policy, and federal agencies would not have the jurisdiction to enforce compliance with the institutional policy. Also of note, a doctor's failure to obtain informed consent prior to performing a medical procedure — whether experimental or not — may give rise to one or more causes of action under state law, enabling the patient to sue for battery and/or malpractice.

[25] See, e.g.. cases listed by National Bioethics Advisory Commission, *Ethical and Policy Issues in Research Involving Human Participants*, Aug. 2001, pp. 3-4.

Approach (Responsible Research),[26] the IOM recommended that federal protections such as requirements for IRB approval and informed consent extend to every research project that involves human participants, regardless of funding source or research setting. NBAC also addressed this issue in *Ethical and Policy Issues in Research Involving Human Participants*[27] *(Human Participants).* In 2001, NBAC recommended a unified, comprehensive federal policy embodied in a single set of regulations and guidance that would apply to all types of research involving human participants (which would unify the requirements of Common Rule, FDA regulations and HIPAA) and legislation to create a single independent federal office to lead and coordinate the oversight system.

Clinical Trials in Developing Nations. As the pace and scope of international collaborative biomedical research have increased, longstanding questions about the ethics of designing, conducting, and following-up on international clinical trials have reemerged. Some of these issues have taken center stage because of the concern that research conducted by investigators and sponsors from more prosperous nations in poor nations that are heavily burdened by disease may, at times, be seen as imposing ethically inappropriate burdens on the host country and on those who participate in the research trials.[28] In its April 2001 report, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*,[29] NBAC referred to these poor nations in which research is increasingly being conducted as *developing* countries, where local technical skills and other key resources are in relatively scarce supply. The following factors are among those that NBAC cited as often leading to bioethical dilemmas posed by research conducted in developing nations:

- Special challenges arise from the combined effects of different countries' distinctive histories, cultures, politics, judicial systems, and economic situations.
- In countries in which extreme poverty afflicts so many, primary health care services generally are inadequate, and a majority of the population is unable to gain access to the most basic and essential health products and services, so the people in these countries are often more vulnerable in situations (such as clinical trials) in which the promise of better health seems to be within reach.
- Making a determination about the appropriate design for a clinical trial depends on various contextual considerations, so that what might be an ethically acceptable design in one situation could be problematic in another. For example, it might be unethical to

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[26] Committee on Assessing the System for Protecting Human Research Participants, Institute of Medicine, *Responsible Research: A Systems Approach*, (Washington: National Academies Press, 2002).

[27] NBAC, *Ethical and Policy Issues in Research Involving Human Participants*, Aug. 2001.

[28] NBAC, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*, Apr. 2001, letter of transmittal to the President.

[29] NBAC, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*, Apr. 2002.

conduct a clinical trial for a health condition in a country in which that condition is unlikely to be found. In comparison, the same trial might be quite appropriately conducted where the trial results could be important to the local population.

- In some countries, the methods used in United States — based studies for identifying appropriate groups for study, enrolling individuals from those groups in a protocol, and obtaining informed voluntary consent might not succeed because of different cultural or social norms. Meeting the challenge of developing alternative methodologies requires careful attention to the ethical issues involved in recruiting research participants and obtaining their consent, which is necessary in order to ensure justice in the conduct of research and to avoid the risk of exploitation.

Discussions among those in the bioethics community have focused on the question of whether the existing rules and regulations that normally govern the conduct of United States investigators or others subject to United States regulations remain appropriate in the context of international research, or whether they unnecessarily complicate or frustrate otherwise worthy and ethically sound research projects. Presently, regardless of where human subjects research is conducted (domestically, in a foreign country, or in a developing nation), the Common Rule's requirements apply if it is funded by a United States agency that has adopted the Rule. In such cases, a department or agency head may approve the substitution of comparable foreign procedures in lieu of those required by the Common Rule. (45 CFR 46.101(h)) Since 1991, no such substitution appears to have been made.[30] The questions raised by NBAC and others are, what standards should such a Department or Agency head use to determine whether foreign procedures are comparable — and is the comparability of standards always necessary?

Fewer questions have been raised regarding the application of FDA's and the Privacy Rule's regulations to research in developing nations. Whether clinical trials are carried out within the United States or abroad, FDA only regulates those that are conducted under an investigational new drug application (IND), which is FDA's approval for a sponsor to conduct a clinical trial. However, by contrast to the Common Rule's requirements, even if a foreign trial were not conducted under an IND, FDA regulations would allow it to be used to support an FDA new drug application (NDA — which is required to market a drug in the United States), if it was conducted in accordance with the principles articulated in the Helsinki Declaration, or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual.[31] (21 CFR

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[30] In March 2005, OHRP posted for public comment a framework for comparing oversight of research involving human subjects in foreign institutions with United States protections. (70 Federal Register 15322 [Mar. 25, 2005])

[31] The Declaration of Helsinki is available online at [http://www.wma.net/e/policy/b3.htm], visited Apr. 11, 2005. In June 2004, FDA issued a new proposed rule, which, if adopted, would replace the requirement that foreign studies be conducted in accordance with ethical principles stated in the Declaration of Helsinki with a requirement that the studies be (continued...)

312.120) The HIPAA Privacy Rule would not likely apply to a study conducted in a developing nation (unless it involved a domestic covered entity handling personally identifiable health information), and has no special provisions relating such research.

Center Watch, a clinical trials listing service, has reportedly found that 20%-30% of clinical trials are being conducted in developing nations.[32] Between 1995 and 1999, the percentage of NDA submissions to FDA using foreign data rose from 9% to 27%, and the number of foreign persons participating in NDA clinical trials rose from 4,000 to 400,000, by one estimate.[33] A variety of articles have explored issues and efforts involved with these trials.[34] Companies reportedly favor clinical trials in developing nations, because it is easier to find patients and physicians who are eager to participate, and less expensive because there are fewer regulatory demands. Some foreign patients may see clinical trials as their best chance for medications. Foreign doctors may find participation appealing because of money they can get as clinical investigators and free medical equipment supplied by drug companies.

Ethical issues involved in international clinical trials can be complicated by the intersection of different social and cultural norms, clinical practices, applicable rules, and regulatory bodies.[35] Commentators have noted the importance of addressing these differences equitably, particularly when a proposed clinical trial is to be conducted in a developing nation where less robust subject protections may be in place.[36]

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[31] (...continued)
conducted in accordance with good clinical practice, including review and approval by an independent ethics committee. (*FDA Proposed Rule:* "Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application," 69 Federal Register 32467 (June 10, 2004).

[32] Information about CenterWatch is available from [http://www.centerwatch.org/aboutcw.html], visited Apr. 11, 2005.

[33] Melody Lin, Deputy Director of OHRP, Director of OIA, "Future Directions for Human Subject Protections in International Research," *Presented in* Sofia, Bulgaria, June 3-6, 2003, at [http://www.uic.edu/sph/glakes/global/conferences/sofia2003/pres/LINpresentation3.pdf], visited Apr. 11, 2005.

[34] For further descriptions of clinical trials in developing nations, see Gina Kolata, "Companies Facing Ethical Issue as Drugs are Tested Overseas," *New York Times*, Mar. 5, 2004, p. A1; Mary Jo Lamberti, "Going Global," *Applied Clinical Trials*, June 1, 2004; Xavier Bosch, "Clinical Trials Partnership Seeks to Boost Research in Developing Countries," *Journal of the American Medical Association,* vol. 292, no. 11 (Sept. 15, 2004), p. 1290.

[35] See, e.g., Marilyn Chase, "Key AIDS Study In Cambodia Now in Jeopardy," *Wall Street Journal*, Aug. 12, 2004, p. B1.

[36] See, e.g., The Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, "Moral Standards for Research in Developing Countries: From 'Reasonable Availability' to 'Fair Benefits'," *Hastings Center Report* ,vol. 43, no. 3 (2004); Lamberti, "Going Global," *Applied Clinical Trials*, Jun. 1, 2004.

The NBAC addressed the topic of clinical trials conducted in developing nations, focusing on whether and how it would be ethical to apply the requirements of the Common Rule made recommendations for the following five areas:[37]

1. The ethical conduct of clinical trials (e.g., review by an ethics committee, individual informed consent, and adequate care for injuries).
2. The selection of research design and the relevance of routine care (e.g., providing care comparable to that in the United States rather than the host country).
3. The fair and respectful treatment of participants (e.g., mechanisms such as consultation with community representatives to inform researchers about cultures and customs of the population from which research participants will be recruited; and culturally appropriate ways to disclose information.)
4. Access to post-trial benefits (e.g., new interventions proven to be effective from the research should be made available to some or all of the host country population beyond the research participants themselves); and
5. The protection of research participant in international clinical trials (e.g., evaluation by HHS's Office for Human Research Protections (OHRP) and host community IRBs).

In 2004, the HHS Secretary's Advisory Committee on Human Research Protections (SACHRP) tasked a subcommittee with investigating issues involved in international research. The subcommittee has yet to issue recommendations.

Human Biological Materials. The Common Rule does not apply to research involving human biological materials[38] (unless the research also involves the humans themselves), so this research may be conducted with federal funding and without donor informed consent, IRB review of research protocols, or institutional assurances of compliance. Like the Common Rule, FDA's regulations governing the conduct of clinical trials would also not apply to research conducted on biological materials. By contrast, the HIPAA Privacy Rule may apply to some of studies on human biological materials. It would require the informed consent of sample donors if the biological materials were deemed to be personally identifiable health information, and if the research involved handling of that information by a covered entity.

As NBAC noted in *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*[39] *(Human Biological Materials)* biomedical researchers often use human biological materials, such as cells collected in research projects, biopsy specimens obtained for diagnostic purposes, and organs and tissues removed during surgery, in order to facilitate their studies. The use of these materials in

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[37] NBAC, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*, Apr. 2001.

[38] HHS' Office for Human Research Protections (OHRP) affirmed that biological specimens are not human subjects in 2004: "Guidance on Research Involving Coded Private Information or Biological Specimens," *OHRP HHS* (Aug. 10, 2004), at [http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf], visited Apr. 11, 2005.

[39] National Bioethics Advisory Commission, *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*, Aug. 1999.

biomedical research can raise questions similar to those involved in human subjects research, centering upon issues of privacy and informed consent. Privacy can become an issue when the biological materials are identified or coded,[40] because information derived from experimentation on the samples could potentially be linked back to its donor. Informed consent becomes difficult to obtain when the future use(s) of the biological materials is not known at the time of their collection, because researchers cannot provide donors with complete information regarding the undetermined future use(s).

NBAC included an exploration of issues of privacy and informed consent in *Human Biological Materials*. Among NBAC's recommendations was one that NIH's Office for Protection from Research Risks (OPRR), the precursor to HHS's OHRP, should consider research conducted with coded or identified samples to be research on human subjects and regulated by the Common Rule. NBAC also recommended that OPRR consider research conducted with unlinked samples to be regulated by the Common Rule, but eligible for exemption from review, and research conducted with unidentified samples not to be regulated by the Common Rule.[41] If NBAC's proposal were adopted, federally funded research with identifiable samples would require informed consent (including the disclosure of mechanisms to protect records' confidentiality), IRB approval, and institutional assurances of compliance.

Social and Behavioral Research. The Common Rule's requirements, including IRB review and the documentation of informed consent, apply not only to biomedical research, but also to social and behavioral research (SBR). The HIPAA Privacy Rule and FDA's regulations could conceivably also apply to some SBR (if the research were conducted by a covered entity or if it were used to support an FDA application, respectively), however regulatory concerns voiced by those in the SBR community have focused primarily on the impact of the Common Rule.

Regarding the Common Rule, which was designed with a focus on biomedical research, some SBR researchers have questioned whether it should apply to SBR, and have expressed a desire to have regulations regarding their research carved out from the Common Rule.[42] This is primarily due to concerns that IRBs are assembled with biomedical expertise, and a review process focused on that research may not be well suited to review social and behavioral research. SBR researchers claim that unnecessary delays often result because their protocols are not accepted for expedited review, despite their assertion that expedited review would be commensurate with

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[40] *Identified samples* are "linked to personal information in such a way that the person from whom the material was obtained could be identified." *Coded samples* are "supplied by repositories to investigators from identified specimens with a code rather than with personally identifying information." (Source: *Human Biological Materials*).

[41] *Unlinked samples* "lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being." *Unidentified samples* "are supplied by repositories to investigators from a collection of unidentified human biological specimens." (Source: *Human Biological Materials*).

[42] See, e.g., Joan S. Sieber, "Social and Behavioral Research with Human Subjects: Key Issues for SACHRP and OHRP to Consider," *Presentation to the Secretary's Advisory Committee on Human Research Protections*, Washington, D.C., Aug. 8, 2004.

the protocols' level and type of risk (risk may be physical in biomedical research but is usually limited to the areas of confidentiality and privacy for SBR). Those involved with SBR have also stated that the mechanisms IRBs approve for obtaining informed consent in SBR are both overly cumbersome and ineffective in their research, because, they say, the consent process mandated by the Common Rule focuses on documenting consent instead of ensuring informed, voluntary decision-making.

In 2003, a National Academies' National Research Council Panel on Institutional Review Boards, Surveys, and Social Science Research (IRBSSR)[43] recommended that OHRP issue guidance for IRBs about what informed consent requirements are appropriate for various forms of SBR, and about when SBR should be classified as minimal-risk research and eligible for expedited review. The IRBSSR also recommended, among other things, funding research on enhancing privacy protections.[44]

Proposed Legislation affecting the Scope of the Common Rule. H.R. 3594 (108th Congress) would have expanded the scope of the Common Rule (which currently only regulates research funded by a federal agency that has adopted the Rule), to all research that is in or that affects interstate commerce. In addition, public entities and private academic institutions would not have been eligible for federal funding unless they maintained or contracted for a comprehensive and ongoing program to educate investigators and Board members on the protection of human subjects in research. The bill would have also required written attestation that the principal investigator was familiar and agreed to comply with the requirements for protecting human subjects, including informed consent. In addition, the bill would have required that information be provided to the subject on how to contact OHRP to submit questions about the rights of subjects or to report concerns regarding the research.

H.R. 3594 (108th Congress) would have required the HHS Secretary publish a determination in the Federal Register, not later than 18 months after the enactment of the Act, specifying whether there were circumstances in which research that studied human tissue or other types of clinical specimens, or that did not involve any interaction with a living human should have been considered human subject research. For SBR, the bill would have required each institution with an IRB to report annually to the HHS Secretary the number of behavioral or social sciences research proposals reviewed, and would have required the Director of OHRP to consult with experts in biomedical, behavioral, and social sciences research in carrying out his or her duties. In addition, the HHS Secretary would have been required to establish expanded informed consent criteria that provided for the provision of full and complete

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[43] Panel on Institutional Review Boards, Surveys, and Social Science Research, National Research Council of National Academies, *Protecting Participants and Facilitating Social and Behavioral Sciences Research* (Washington: National Academies Press, 2003).

[44] In July 2004, SACHRP heard a series of presentations on protecting human subjects in SBR. Presenters raised issues and made recommendations similar to those of the IRBSSR. These are available online at [http://www.hhs.gov/ohrp/sachrp/mtgings/mtg07-04/present.htm], visited Apr. 11, 2005.

information relevant to the research to a prospective human subject (possibly to allow informed consent to be modified for SBR).

S. 3060 (107th Congress) would have expanded the definition of covered research(which would have triggered the application of all Subparts of 45 CFR 46) to that conducted on human subjects conducted in the United States, funded by the United States government or subject to federal regulatory review. The bill would have established within HHS a National Office of Human Research Protections, headed by a Director to be appointed by the Secretary of HHS. The Director would have been able to promulgate regulations to determine whether various types of research were covered by 45 CFR 46, and whether the research involved greater than minimal risk.

With regard to research conducted overseas, S. 3060 (107th Congress) would have required that the Director publish a list of countries with human research subject protections comparable to those in the United States. Studies conducted in those countries would have been reviewed by an ethics board for compliance. For countries not on the list, the bill would have required review by both an ethics board and an IRB for studies that posed greater than minimal risk to the participants.

Inclusion and Protection of Vulnerable Populations

Participation of vulnerable populations in research raise two types of concerns. First, concerns of inclusion, which focus on the importance of integrating all populations in research on drugs that may be prescribed to them. Second, concerns of protection, which focus on the need to help ensure that vulnerable populations are not coerced into participating in research, or mistreated during their involvement.

The Common Rule provides that IRBs should ensure that the selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons (45 CFR 46.111(a)(3)). In its review of research involving these vulnerable populations, the IRBs must give consideration to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects (45 CFR 46.107(a)). When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards must be included in the study to protect the rights and welfare of these subjects (45 CFR 46.111(b)). For example, a prisoner may feel incapable of refusing a request made by a guard or warden to sign an informed consent document, or a child may be persuaded to do so without truly understanding the meaning of participation in the study. In each of those cases, the subjects may have signed documents, but could not have truly given informed consent. In addition, Subparts B, C, and D of 45 CFR 46 contain specific regulations governing research on pregnant women, prisoners, and children, respectively. FDA regulations contain provisions regulating research on children (21 CFR 50.54,55), and for the conduct of research in emergency situations (21 CFR 50.24). The HIPAA Privacy Rule contains no special provisions with regard to vulnerable populations.

Exclusion of some populations from research has in the past stemmed from the reluctance of both researchers and potential subjects. Researchers have been disinclined to conduct research on diverse populations because they want to reduce as many variables as possible (for example, accepting only subjects with the same race, gender, and age) to streamline their trials. Potential subjects have been afraid to participate in trials because they do not trust investigators, having heard about abuses like those in the Tuskeegee syphilis study.

The NBAC focused some attention on ensuring that all segments of society can participate in research in *Human Participants*, calling for additional appropriate protections for those who may be more susceptible to coercion or exploitation. In order to protect these populations, NBAC recommended that federal policy promote the inclusion of all segments of society in research, that guidance be developed on avoiding harmful or coercive situations, and that sponsors and investigators design research that incorporates appropriate safeguards to protect all prospective participants.

Minorities. None of the federal regulations for the protection of human research subjects (the Common Rule, other Subparts of 45 CFR 46, the Privacy Rule, and FDA regulations) address issues of race. The Common Rule's provision that calls for equity in research subject selection lists prisoners, pregnant women, mentally disabled persons, and economically or educationally disadvantaged persons — but makes no reference to race (45 CFR 46.111(a)(3)). Barriers to the recruitment of African Americans and other minority populations have been noted by a number of researchers, and are reportedly economic, cultural, and trust-based.[45] Such barriers may lead to disparities in health outcomes. For example, African Americans are at a higher risk for stroke, and yet treatment recommendations are based largely on studies involving few African Americans.[46]

To address disparities in minority participation in research as well as a range of other health issues, Congress passed the Minority Health and Health Disparities Research and Education Act of 2000 (P.L. 106-525), elevating the Office of Minority Health Research (created by the NIH Director in 1990) to the level of center, and renaming it the National Center on Minority Health and Health Disparities. The Center works to address and ease health disparities involving cancer, diabetes, infant mortality, AIDS, cardiovascular illnesses, and many other diseases.[47]

Children. The Common Rule requires equity in research subject selection, but also urges IRBs to be particularly cognizant of the special problems of research involving children, among other groups (45 CFR 46.111(a)(3)). The Rule also requires studies including children and other vulnerable populations to include

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[45] Mike Mitka, "Efforts Needed to Foster Participation of Blacks in Stroke Studies," *Journal of the American Medical Association,* vol. 291, no. 11 (Mar. 17, 2004), p. 1312.

[46] DeJuran Richardson *quoted in,* Mike Mitka, "Efforts Needed to Foster Participation of Blacks in Stroke Studies," *Journal of the American Medical Association,* vol. 291, no. 11 (Mar. 17, 2004), p. 1311.

[47] "What We Do," *National Center on Minority Health and Health Disparities*, visited Mar. 1, 2005, at [http://ncmhd.nih.gov/about_ncmhd/what.asp], visited Apr. 11, 2005.

additional safeguards to protect the rights and welfare of these subjects (45 CFR 46.111(b)). A section of regulations that are not a part of the Common Rule, Subpart D of 45 CFR 46, generally specifies that research involving children must involve the assent of the children and the permission of the parents, and contain some added protections for the children.[48] FDA and HHS regulations governing research involving children are not identical, which has led to some problems, and to some recommendations by the IOM and SACHRP.

HHS and FDA regulations. HHS regulations (45 CFR 46 Subpart D — not a part of the Common Rule) and FDA regulations are parallel but not identical regarding the protection of children in research. Both specify that research may be conducted on children if they assent,[49] their parents or guardians consent, and:

- the research involves no more than minimal risk;
- the potential direct benefit to the subjects outweighs the risk to them; or
- the research involves no more than slightly more than minimal risk and is likely to yield generalizable knowledge about the subject's disorder or condition.[50]

These categories are relatively free from controversy, except that guidance has been requested regarding what constitutes *minor increase over minimal risk*.[51] However, there is one other, more controversial category of allowable research on children: research with a *407 determination*, so named because of the section of HHS regulations that govern it. This research:

- is not eligible for conduct under any other provision (of HHS human subjects protection regulations);
- involves more than minimal risk to subjects;
- does not present the prospect of direct benefit to the individual subjects; *and*
- is not likely to yield generalizable knowledge about the subjects' disorder or condition; *but*

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[48] In 1997, the Department of Education (ED), which has a particular interest in research involving children, adopted *Subpart D — Additional Protections for Children Who Are Subjects in Research*. (35 CFR 97.401-409; adopted in 62 Federal Register 63221 (Nov. 26, 1997]) ED has also adopted the Common Rule (Subpart A), but has not adopted Subparts B or C.

[49] The term *assent* is used to describe a child's agreement to participate in research. By contrast, *consent* means not only agreement, but agreement that is based upon consideration with a level of mental capacity and experience that the law generally does not presume a person is capable of forming until reaching the age of majority. Therefore, the *assent* of a child must be accompanied by the *consent* of a guardian.

[50] 45 CFR 46.404-406 (HHS) and 21 CFR 50.51-53 (FDA).

[51] Secretary's Advisory Committee on Human Research Protections, Alexandria, VA, Mar. 2004.

- presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.[52]

In addition to IRB approval, studies meeting the criteria for a 407 determination must also gain approval from the HHS Secretary and/or FDA Commissioner, depending on which regulations apply to the research. The approval process involves consultation with a panel of experts in pertinent disciplines and an opportunity for public review and comment. Like other studies involving children, the assent of the subjects and consent of their parents is also required.

To help clarify the approval process in HHS, the HHS Secretary requested that SACHRP recommend a procedure for conducting 407 reviews. In March 2004, SACHRP voted to recommend that, following an IRB request for 407 review, the HHS's Office for Human Research Protections (OHRP) should screen the application to determine if a 407 designation is appropriate. If so, SACHRP asserted, OHRP should appoint a non-FACA[53] panel for the Secretary, consisting of experts in science, ethics, pediatrics, and the disorder/condition under the study; and at least one public member who can adequately represent and voice the interests of the subjects.[54]

To assist the FDA with the approval process and other matters, in August 2004, the FDA announced establishment of the Pediatric Ethics Subcommittee. The Subcommittee will address pediatric ethical issues, as well as IRB referrals to clinical investigations involving children as subjects and IRB referrals that involve both FDA regulated products and research involving children as subjects that is conducted or supported by HHS.[55]

IOM Report. As requested in the *Best Pharmaceuticals for Children Act of 2002* (P.L.107-109) the HHS Secretary contracted with IOM to generate a report about clinical research involving children. The report, entitled *Ethical Conduct of Clinical Research Involving Children*, was published in March 2004, and contained the following recommendations:[56]

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[52] 45 CFR 46.407 (HHS) and 21 CFR 50.54 (FDA).

[53] The Federal Advisory Committee Act (FACA) defines how federal advisory committees operate. For further information, see CRS Report RL30260, *Federal Advisory Committees: A Primer*, by Stephanie Smith.

[54] Ernest Prentice, "Update on HHS Advisory Committee on Human Research Protection," presented at the Fourth National Medical Research Conference, Baltimore, MD, Apr. 23, 2004. These recommendations were reiterated in SACHRP Subcommittee involving Children, "Draft for Subcommittee Review and Comment, Meeting Held Jun. 15, 2004," presented to the Secretary's Advisory Committee on Human Research Protections, July 2004, Washington, DC.

[55] HHS, FDA, "Advisory Committee; Pediatric Advisory Committee; Formation of a Pediatric Ethics Subcommittee," 69 Federal Register 46153 (Aug. 2, 2004).

[56] Committee on Clinical Research Involving Children, Board on Health Sciences Policy, Institute of Medicine, *The Ethical Conduct of Clinical Research Involving Children* (Washington: National Academies Press, 2004).

- researchers and reviewers should evaluate research involving minimal risk, minor increase over minimal risk, or specific health, emotional or mental conditions in relation to every-day activities of children;
- IRBs should ensure that there is an ongoing informed consent process (accompanying the legally required informed consent documentation) that meets the needs of multi-cultural or multilingual families, those with severely injured children, and research that qualifies for a waiver of parental permission;
- IRBs should make sure that researchers implement a process for requesting children's assent and parental permission that are developmentally appropriate to children and clarify parents' roles in decision-making;
- IRBs, sponsors, and research institutions should adopt written policies regarding payment for children's participation in research, specifying acceptable and unacceptable amounts and types of payments;
- HHS should develop and implement a plan for data collection and regulatory refinement for research involving children;
- organizations that accredit human research protection programs should incorporate requirements specific to research on children;
- Congress should enact a Federal law that governs all research involving children; and
- federal and state legislators should help support the development of experts, materials, and resources about research in children.

Children who are Wards. In the spring of 2005, interest in research involving children who are wards was generated by news reports that, in the 1980s, NIH-funded studies tested antiretroviral AIDS therapies on HIV-positive foster children. Concerns were raised that researchers had not provided the children with the protections required for HHS-funded research or those that the research institutions had promised to use, such as the appointment of advocates for the children.[57] Others stressed the positive points of the foster children's inclusion – that it ensured that they received some treatment for HIV (at a time when there was no approved therapy) from world-class researchers at government expense, slowing their rate of death and extending their lives.[58] The controversy highlighted the fundamental balance sought between wards' and other vulnerable populations' protection and inclusion in research: ensuring that those in vulnerable positions are adequately shielded from coercion and abuse, with a process not so cumbersome that it *de facto* excludes them from research. On May 18, 2005, the House Committee on Ways and Means: Subcommittee on Human Resources held a hearing on Protections for Foster Children Enrolled in Clinical Trials to investigate the issue.

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[57] *See, e.g.*, John Solomon, "Federal Researchers Tested AIDS Drugs on Foster Children Without Basic Protection," *Chicago Sun-Times*,May 5, 2005, at [http://www.suntimes.com/output/health/cst-nws-aids05.html], visited May 31, 2005.

[58] Ibid.

The Common Rule and the HIPAA Privacy Rule neither define nor use the terms ward or guardian. While 45 CFR 46 also contains no definition of ward, subpart D uses the term in the clause "children who are wards of the State or any other agency, institution, or entity..." (45 CFR 46.409). Subpart D of 45 CFR 46 defines the term guardian as an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care (46.402(e)). (Subpart D, described in the preceding section on *Children*, provides additional protections for children who are research subjects. Subpart D is not a part of the Common Rule, but it has been adopted by the Department of Education, and FDA has adopted parallel provisions in its own Subpart D.)

FDA defines the term *ward* as a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law (21 CFR 50.3(q)). FDA defines the term *guardian* as an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. For purposes of Subpart D, FDA's definition of guardian also includes individuals authorized to consent on behalf of a children to participate in research (21 CFR 50.3(s)).

Wards who participate in research may have three layers of federal protection, none of which would attach unless the research were federally funded or conducted for FDA submission. First, both the Common Rule and FDA regulations contain basic protections, noted in the *Introduction* to this report, that would apply to research involving children who are wards, just as they apply to all covered human subjects research. Second, the protections for children included in Subpart D would lend additional protections to children who participate in covered research, including wards.

Third, a provision in subpart D of both 45 CFR 46 and FDA regulations, which provides special protections for wards (45 CFR 46.409; 21 CFR 50.56), may also apply. The provision is triggered by the following two types of research conducted on children who are wards: (1) that involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR 46.406; 21 CFR 50.53); and (2) that not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407; 21 CFR 50.54). If triggered, the wards provision has two requirements: (1) that wards be included only if the research is related to their status as wards, or is conducted in settings in which the majority of children involved as subjects are not wards; and (2) that the IRB require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate is to be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

Prisoners. Those seeking to protect prisoners are wary of research on this population because their lack of liberty and choice may interfere with their ability to give meaningful consent. On the other hand, overly-stringent requirements can prevent research that could be particularly effective for and/or in prison populations, such as those related to transmission of the human immunodeficiency virus (HIV).

The Common Rule provides that when some or all of the subjects are prisoners or members of other vulnerable populations, additional safeguards must be included in the study to protect the rights and welfare of these subjects (45 CFR 46.111(b)). Research involving prisoners that is funded by HHS is also governed by Subpart C of 45 CFR 46 (not a part of the Common Rule): *Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects*.[59] Subpart C requires researchers working with prisoners to provide extra assurances that the protocol is fair and that participation is not coerced through mechanisms such as arbitrary intervention by prison authorities, or the offering of possible advantages of such a magnitude that the prisoner's ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired (45 CFR 46.305(a)). The HHS Secretary must confirm that the purpose of the study is generally focused on prisoners, prisons and/or incarceration. (45 CFR 46.306 (a)(2)). In addition, the IRB carrying out responsibilities under Subpart D with respect to research involving prisoners is to have a majority of members with no association with the prison(s) involved, and at least one member who is a prisoner or a prisoner representative, except that where a particular research project is reviewed by more than one IRB, only one Board need satisfy this requirement (45 CFR 46.304). Neither FDA regulations nor the HIPAA privacy rule have provisions focused on research with prisoners.

A SACHRP subcommittee has reviewed Subpart C, and recommended that it be totally revised to ensure that regulations do not obstruct ethically and scientifically appropriate research involving prisoners for the benefit of prisoners and others.[60] However, having recognized that a total revision of Subpart C will take time, the subcommittee recommended that, as an intermediate solution, the following portions of the existing regulation be clarified:

- the definition of prisoner — making it functional (so that it might include, for example, persons in community corrections programs, on probation, or on parole) rather than contingent on classifications of incarceration;
- the applicability of Subpart C when incarceration occurs

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[59] In 1994, the Department of Justice's Bureau of Prisons, which has a special interest in conducting research involving prisoners, adopted its own regulations regarding research involving prisoners (*Subpart B — Research*), which are similar to, though more rigorous than 45 CFR 46, Subpart C. (28 CFR 512.10-21; adopted at 59 FR 13860, Mar. 23, 1994, as amended at 62FR 6661, Feb. 12, 1997) The Department of Justice (DOJ) has adopted the Common Rule (Subpart A of 45 CFR 46). DOJ has not adopted 45 CFR 46's Subparts B-D.

[60] Ernest D. Prentice, "Update on HHS Advisory Committee on Human Research protection," presented at the Fourth National Medical Research Summit, Baltimore, MD, Apr. 23, 2004.

- post-enrollment;
- the necessary qualifications of the prisoner representative on the IRB;
- the scope of follow up care required after a study ends, when incarceration ends or when it continues.[61]

Pregnant Women, Human Fetuses, and Neonates. The establishment of appropriate rules to govern research on pregnant women, fetuses and neonates involves balancing protections with requirements. Protections are necessary to minimize the risk of harm, particularly given that neonates and fetuses are unable make decisions about whether to participate in research. Requirements are necessary to help ensure that treatments for women, fetuses and neonates are developed, and that researchers do not avoid testing on these populations because of fear of harm to the subjects and the potential for resulting litigation.

FDA regulations and the HIAA Privacy Rule have no special provisions pertaining to research involving pregnant women, fetuses, or neonates. However, the Common Rule provides that when some or all of the subjects are pregnant women or other vulnerable populations, additional safeguards should be included in the study to protect the rights and welfare of these subject (45 CFR 46.111(b)). In addition, HHS regulations that are not a part of the Common Rule contain specific protections for women, human fetuses, and neonates (45 CRF 46, Subpart B). Subpart B was amended in 2001 to include additional protections for pregnant women, human fetuses, and neonates.[62] Subpart B now instructs IRBs to make determinations based on a combination of factors, such as whether there is the potential for a direct benefit to the woman, fetus, or neonate, whether there is more than a minimal level of risk, and whether the neonate is viable (45 CFR 46.203-206). Neither the Common Rule, nor Subpart B apply to embryonic research performed outside of the uterus, to in vitro fertilization.[63]

In a continuing effort to strike the best regulatory balance, the HHS Secretary has requested that SACHRP advise the HHS Secretary and OHRP on whether Subpart B appropriately protects pregnant women, fetuses, and neonates in

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[61] Subpart C Subcommittee, "Issues Identified for Possible Short or Intermediate Term Solutions," presented to the Secretary's Advisory Committee on Human Research Protections meeting, Alexandria, VA, Mar. 2004; Subpart C Subcommittee, "DRAFT - Subpart C," presented to the Secretary's Advisory Committee on Human Research Protections meeting, Washington, DC, July 2004, at [http://www.hhs.gov/ohrp/sachrp/mtgings/mtg07-04/present/subpartc_files/frame.htm], visited Apr. 11, 2005.

[62] 66 Federal Register 56776, Nov. 13, 2001.

[63] The Dickey Amendment (a rider that Congress has attached annually to the Labor, HHS, and Education appropriations acts from FY1996 to the present) prohibits HHS from using appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. For further information about the Dickey amendment and other restrictions related to embryo research, *see* CRS Report RL31015, *Stem Cell Research*, by Judith A. Johnson and Erin D. Williams.

consideration of the Belmont Principles of Beneficence, Justice, and Respect for Persons.[64] SACHRP's work on the topic is ongoing.

Diminished Capacity. Diminished capacity for decision-making (a lessened ability to make or express one's autonomous choices) can be caused by permanent conditions, such as dementia or retardation, as well as temporary situations, such as accidents or emergencies that render victims unconscious for a time. Research on populations with diminished capacity is complicated by the fact that potential participants may not be capable of understanding and evaluating options, which are necessary to be able to give informed consent. On one hand, some feel that restrictions should be strong enough to protect members of the vulnerable populations from abuse, which they may not be capable of avoiding or addressing due to their diminished capacity. On the other hand, some note that if research on these populations is restricted, treatments for emergency situations or for diseases such as Alzheimer's may never be pursued.

The HIPAA Privacy Rule contains an emergency use provision that allows for disclosures to be made in some narrow circumstances without prior authorization if authorization cannot practicably be provided because of the individual's incapacity or because of an emergency treatment circumstances (45 CFR 164.510(a)(3)) .[65] The Common Rule allows for consent to be given by a subject's legally authorized representative (LAR — persons empowered to give informed consent on behalf of potential subjects with diminished capacity), and contains some exceptions to the requirement that informed consent be documented (45 CFR 46.116 and 117(c)). In addition, it allows an IRB to waive the requirement of an informed consent procedure if it determines that (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation (45 CFR 46.116(c)) . By contrast to the Common Rule,[66] FDA regulations specifically allow for research to be conducted without consent in emergency situations in which taking the time to obtain the consent of either the subject or of his or her LAR would prove detrimental to the subject (21 CFR 50.24).[67] In June 2004, HHS published an advance notice of

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[64] Ernest Prentice, "45 CFR 46 Subpart B Additional Protections for Pregnant Women, Human Fetuses & Neonates Involved in Research," *Presentation to the Secretary's Advisory Committee on Human Research Protections*, (July 27, 2004), Washington, DC.

[65] In November 1978, DHEW (HHS's predecessor) published *Proposed Regulations on Research Involving Those Institutionalized as Mentally Disabled*, at 43 Federal Register 53,950 (Nov. 17, 1978). The proposed regulations were never adopted.

[66] In 1997, President Clinton issued a memorandum to 19 Department and Agency heads prohibiting the waiver of informed consent for classified research, among other things. "Strengthened Protections for Human Subjects of Classified Research" *Presidential Memorandum* (May 13, 1997), 10 U.S.C. § 1107, available at [http://www.eh.doe.gov/ohre/roadmap/whitehouse/appe.html].

[67] On October 2, 1996 (61 Federal Register 51531), the Secretary, HHS, announced, under Section 46.101(i), a waiver of the applicability of the 45 CFR Part 46 requirement for

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proposed rulemaking on the topic: *Additional Protections for Adults with Impaired Decisionmaking Capacity*. (69 Federal Register 37473 [June 28, 2004]).

In 1998, the NBAC investigated the topic of research on populations with diminished capacity.[68] Its report included extensive recommendations for the selection of LARs, and the criteria the representatives should use to make surrogate decisions. In addition, NBAC recommended the following for research involving persons with diminished capacity:

- it should only be performed if other populations (without diminished capacity) could not be used;
- protocols should include procedures designed to minimize risks to subjects;
- an IRB may waive the informed consent requirement if a study involves no more than minimal risk; and
- researchers may conduct studies involving more than minimal risk and no direct benefit to the subjects if they first obtain an evaluation by a special panel convened by the HHS Secretary.

Proposed Legislation Affecting the Inclusion and Protection of Vulnerable Populations in Research. H.R. 3594 (108th Congress) would have required all research that was federally regulated and/or affected interstate commerce to be conducted in accordance with 45 CFR 46 (including Subparts B-D which provide special protections for certain vulnerable populations).[69] In other words the vulnerable populations protections contained in 45 CFR 46 would have been applied to research conducted, funded or regulated by a federal agency — whether or not they had previously adopted the Common Rule — and to those conducting research that affects interstate commerce (meaning virtually all researchers in the United States). This would have greatly expanded the reach of federal regulations governing research with vulnerable populations.

On the topic of diminished capacity, not later than three years after the enactment of the Act, the HHS Secretary would have been required to promulgate

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[67] (...continued)
obtaining and documenting informed consent for a strictly limited class of research, involving research activities that may be carried out in human subjects who are in need of emergency therapy and for whom, because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be obtained. This provision applies only to HHS research and is not a part of the Common Rule. See Gary B. Ellis and Melody Lin, "Subject: Informed Consent Requirements in Emergency Research," *OPRR Reports*, [no. 97-01], (Oct. 31, 1996), at [http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc97-01.htm], visited May 3, 2005.

[68] NBAC, *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*, Dec. 1998, at [http://www.georgetown.edu/research/nrcbl/nbac/capacity/Executive.htm], visited Apr. 11, 2005.

[69] In cases in which both FDA and Common Rule regulations might apply, H.R. 3594 (108th Congress) would have clarified that FDA's definitions of *vulnerable populations* would prevail. (H.R. 3594, proposed § 491A(b)(1)(C))

regulations to enhance the protection of people with diminished decision making capacity with respect to their participation as subjects in human subject research. In addition, within 18 months of the enactment of the Act the Secretary would have been required to complete a review of areas of difference between HHS and FDA regulations on the topic of research relating to emergency interventions (which would have often applied to persons with a diminished capacity for decision making), among other things. Within that same time frame, the Secretary would have also been required to publish a determination in the Federal Register regarding (i) whether modified procedures should have applied to human subject research that posed minimal risk to the subjects, including whether there were any types of such research for which some aspect of the requirement of informed consent or documentation of informed consent should have applied differently, and (ii) whether the list of expedited procedures or the list of exemptions under the Common Rule should have been modified or new categories of expedited procedures established. This may have helped to create specific rules governing research on both persons with diminished capacity and children.

Like H.R. 3594, S. 3060 (107th Congress) would have extended all of the Subparts of 45 CFR 46 to all research conducted in the United States, funded by the United States government or subject to United States regulatory review. For subjects who underwent trauma and could not practically consent (one population with a diminished capacity for decisionmaking), alternative means of obtaining consent would have been sought as described in the FDA regulations, 21 CFR 50.24.

Institutional Review Boards (IRBs)

The Common Rule and FDA regulations charge IRBs with reviewing protocols for human subjects research to ensure that the studies will be conducted with proper protections for human subejcts. The HIPAA Privacy Rule relies either upon IRBs or separate Privacy boards to carry out its function of protecting subjects' health information. Questions have been raised regarding IRBs' membership, responsibilities, and duties, and the extent of their registration with the federal government.

IRB Membership. IRB deliberations require expertise in both the scientific underpinnings of proposed research and also in local customs and understandings associated with being a research subject. Some have expressed concern regarding the potential for bias in IRB deliberations when most members are affiliated with the institution or company conducting research, and may have a vested interest in the outcome.[70] Finding the appropriate balance is important to ensure the scientific validity of the study design while incorporating concerns of subjects.

The Common Rule (45 CFR 46.107) and FDA regulations (21 CFR 56.107) for IRB membership are identical. The HIPAA Privacy Rule refers to IRBs and to the

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[70] See, e.g., M. Cho and P. Billings, "Conflict of Interest and Institutional Review Boards," *Journal of Investigative Medicine*, vol. 45, no. 4 (1997), pp. 154-159; S. Peckman, "Local Institutional Review Boards," in NBAC *Ethical and Policy Issues in Research Involving Human Participants*, vol. 2 (Bethesda, MD: NBAC, 2001).

Common Rule, but does not create new requirements for IRB membership. It does, however, list the requirements of a privacy board's membership — and many institutions have their IRB serve as their privacy board. The HIPAA privacy board membership requirements are a subset of the Common Rule's requirements for IRB membership (45 CFR 164.512(i)(1)(i)(B)).

In order to protect against the potential for pro-institution or pro-industry bias in IRB deliberations, the IOM (in *Responsible Research*) and the NBAC (in *Human Participants*) recommended that at least 25% of the IRB membership comprise people unaffiliated with the institution, and at least 25% comprise non-scientists. If adopted, these recommendations would increase the Common Rule's current requirement that an IRB have at least one member (of a minimum of five members) from each of these categories. In addition, IOM and NBAC recommended that a new requirement be added that at least 25% of an IRB's members represent the local community and/or the participant perspective. NBAC further recommended that federal regulations specify standards that individuals must meet to be included on an IRB.

IRB Duties. According to the Common Rule and FDA regulations, an IRB is tasked with the responsibility for protecting the rights and welfare of human subjects. Increases in the scope of responsibility and number of protocols that IRBs review have limited the depth with which some IRBs are able to consider human subjects protocols. IRBs may find themselves tasked not only with protecting human subjects, but also with other duties such as regulatory compliance, risk management, conflict of interest reviews, and carrying out the functions of a HIPAA privacy board.[71]

In *Responsible Research*, IOM noted that overloading IRBs, whose members are generally not paid for their participation, "is a disservice to research participants." It recommended that the IRB focus its full committee deliberations and oversight primarily on the ethical aspects of the protection of research subjects. Specifically, it recommended that IRBs not be tasked with responsibilities that the Common Rule does not require (e.g., managing institutional risk, ensuring institutional compliance with all relevant research rules and regulations, and assessing potential conflicts of interest with other units within the research program or organization), and that these be assigned to other oversight bodies within an institution.

IRB Registration. By some estimates, there are at least five thousand IRBs in the United States, but the exact figure is unknown because they are not all required by the Common Rule,[72] FDA regulations,[73] or the HIPAA Privacy Rule[74] to register

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[71] A privacy board reviews a covered entity's preparatory research that involves personal health information to determine whether privacy protections are adequate (45 CFR 164.512(i)(1)(i)(B)).

[72] OHRP gathers information about some IRBs under the terms of the Common Rule. If an institution seeking federal funding opts to obtain a federal-wide assurance (which a funding Federal Department or Agency must accept in lieu of the direct submission of an assurance), the institution must provide information about its IRB (among other things) to OHRP. If the (continued...)

in a central location. In 1998, the HHS Office of the Inspector General (OIG) issued several reports on IRBs, one of which contained the recommendation that IRBs register with the Federal government.[75] OHPR reviewed the OIG's recommendations, concluded that registration would be highly beneficial for identifying, monitoring, and tracking IRBs for outreach activities, and began registering IRBs in December 2000. OHRP required, among other things, a list of IRB members, their representative capacities, and experience, and their employment or other relationship(s) with the institution. OHRP currently posts all registered IRBs on its website.[76]

On July 6, 2004, OHRP published a proposed rule in the Federal Register[77] that would create one IRB registration system for HHS (including both OHRP and FDA), administered at a single website. The proposed new rule would require institutions to provide additional information that OHRP currently requests but does not require. This includes, for example, information regarding the accreditation status of the institution or IRB organization, total numbers of active research protocols reviewed by the IRB (including protocols supported by other Federal departments or agencies) and the nature of those protocols, and IRB staffing.

Defining and Weighing Risks and Potential Benefits. Two of an IRB's primary responsibilities are to define and weigh a study's risks and potential benefits. The Common Rule and FDA regulations similar advice to IRBs on this topic. The HIPAA Privacy Rule refers to the sections of the Common Rule that address risk,[78] but does not raise new issues on the topic.

The Common Rule and FDA regulations both define *minimal risk* in the same way. (45 CFR 46.102(i) (HHS); 21 CFR 50.3(f) (FDA)) However, the FDA regulations and 45 CFR 46 Subpart D (which does not include the Common Rule) use but do not define not define the term *minor increase over minimal risk* (45 CFR

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[72] (...continued)
institution does not seek a federal-wide assurance, it is required to submit such information to the funding Department of Agency head rather than to OHRP (45 CFR 46.103(a); (b)(2)).

[73] FDA could gather information about IRBs that review protocols for submission to FDA. FDA requires IRBs to keep records and make them available for FDA inspection (21 CFR 56.115).

[74] The HIPAA Privacy Rule requires privacy boards and IRBs to keep records, but not to register at a centralized location (45 CFR 164.512(i)(1)(i)(B)).

[75] OIG, HHS, *Institutional Review Boards: A Time for Reform*, June 1998, at [http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf], visited Apr. 11, 2005.

[76] Office of Public Health and Science, HHS, *Institutional Review Boards: Registration Requirements*, 69 Federal Register 40585 (July 6, 2004). The current OHRP IRB registration form is available at [http://www.hhs.gov/ohrp/humansubjects/assurance/regirb.htm], visited Apr. 11, 2005.

[77] Office of Public Health and Science, HHS, "Institutional Review Boards: Registration Requirements," 69 Federal Register 40585 (July 6, 2004).

[78] See, e.g., 45 CFR 164.512(i)(2)(iv)(a): "(A) An IRB must follow the requirements of the Common Rule, including the normal review procedures. ..."

46.406(a) (HHS); 21 CFR 50.53(a) (FDA)). In addition, both FDA regulations and 45 CFR 46 (including the Common Rule) leave the weighing of risks and potential benefits in individual protocols up to local IRBs, enabling them to apply local community standards. Thus, the IRB must discern what factors should be considered in the risk/benefit equation.

One way potential benefits from research may be categorized is by their likely recipients. A research study might have potential benefits for the research subjects, for people in the same category as the research subjects, and/or for society in general.[79] Despite general ethical prohibitions against putting one group of people at risk solely for the benefit of others, many observers have found that some small amount of risk might be acceptable even if there is no predicted benefit to the subjects. The National Research Council of the National Academies (NRC) considered whether researchers could expose subjects to small amounts of pesticides that are currently in use in order to establish their safety.[80] Such a study would pose some (minimal) risk to the subjects, but no potential benefit would flow to them or to others in the same category. The only benefit would accrue to society. In this case, the NRC found that health and environmental benefits to society could justify "a somewhat higher risk level than that posed by studies for which there is no identifiable risk or for which there is a reasonable certainty of no harm." NRC stressed that a risk of lasting harm is never justifiable.[81]

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[79] For example, a study with potential benefits for *research subjects* could be one conducted on a child with leukemia designed to diminish the effects of his/her disease. A study with potential benefits for *individuals in the same category as research subjects* could be an observation of the disease process of leukemia in children. Such a study would not be designed to benefit the children in the study, but rather to facilitate the future development of treatments for other children with leukemia. A study with potential benefits for *society* could be taking blood from children with leukemia in order to help develop a vaccine unrelated to children or to leukemia. Such a study would not be designed to benefit the children in the study or other children with leukemia, but rather society in general.

[80] NRC, *Intentional Human Dosing Studies for EPA Regulatory Purpose* [Advance Copy], released on Feb. 19, 2004.

[81] In a move that touched on the topic of weighing risks and potential benefits involved in pesticide research, in Apr. 2005, the acting administrator of the Environmental Protection Agency (EPA) cancelled a program (the Children's Health Environmental Exposure Research Study) that was "designed to fill critical data gaps in the understanding of how children may be exposed to pesticides (such as bug spray) and chemicals currently used in households." [http://www.epa.gov/cheers/], visited Apr. 13, 2005. The cancellation was made following accusations that the study would have created unacceptable health risks to children and disproportionate risks to low-income children among other things. See, e.g., [http://www.ibiblio.org/arc/programs/cheers.html], visited Apr. 13, 2005.

In the cancellation notice, the EPA Acting Administrator noted that many misrepresentations about the study had been made, and added that EPA must conduct quality, credible research in an atmosphere absent of gross misrepresentation and controversy.

On a related note, in Feb. 2005, the EPA published a proposed plan to establish a comprehensive framework for making decisions about the extent to which it will consider or rely on certain types of human subjects research, including that with pesticides. The plan included a statement of EPA's intention to pursue rulemaking, in which it may adopt all

(continued...)

Others have voiced disagreement with NRC's position, stating pesticide experiments in human beings are "morally unconscionable and scientifically dubious - they fail to meet fundamental standards of permissible research - as they offer no potential therapeutic benefit to the subjects or society."[82] Opponents of pesticide experimentation also claim that such experiments violate the Nuremberg Code and all subsequent national and international codes of medical research ethics that were adopted precisely to prevent potentially harmful experiments from ever again being conducted on human beings.[83]

A parallel issue to whether studies with no therapeutic value and minimal risk may be ethically conducted, is whether study participants can ethically be denied known treatments and be placed on a placebo as a part of a control group in the investigation of a new drug or treatment. While participation may benefit subjects who receive the new drug, those in the placebo group may not benefit, and may actually undergo some risk if denied a known treatment by their participation in the study. According to ethicist Howard Brody, researchers may "deny part of the study group a treatment known to be effective [as long as] subjects are not harmed in seeking the goal of gaining new knowledge."[84] The NBAC drew a finer distinction in *Human Participants*, stating that when placebos are used (and in all cases), IRBs should limit the amount of social and physical risk that can be imposed, regardless of the participants' willingness to participate or the monetary (or other) enticement being offered. Further, the possibility of some benefit from one element of a study should not be used to justify otherwise unacceptable elements of research whose potential benefits, if any, accrue solely to society at large.

Unlike the difficulty with estimating potential benefits, which rests in part on the likely recipient, the difficulty with risk assessment lies in ensuring that the level of risk triggers an appropriate level of review. Thorough review of protocols that pose minimal risks to human participants may be conducted quickly, while those with higher risk may require more scrutiny. As the number and variety of research protocols involving human subjects has increased, some IRB members have called for consistent, transparent guidance about oversight required for various categories of human subjects research.

The NBAC addressed this issue in *Human Participants*, recommending that Federal policy require an ethical review that is commensurate with the nature and level of risk involved, and defining minimal risk as the probability and magnitude of

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[81] (...continued)
subparts of 45 CFR 46 (70 FR 6661, Feb. 8, 2005). EPA adopted the Common Rule in 1991.

[82] Testimony of Alliance for Human Research Protection President and Founder, Vera Hassner Sharav, to the *Committee on the Use of Third Party Toxicity Research with Human Research Participants, Science, Technology, and Law Program*, at NAS (Jan 8, 2003), at [http://www.ahrp.org/testimonypresentations/EPApesticide.php], visited May 3, 2005.

[83] See ibid.

[84] Scott C. Jenkins, "Placebo Ethics Depend on Informed Consent, Scientific Value, Michigan State's Brody Asserts," *Washington Fax* (Feb 23, 2004), p. 1.

harms that are normally encountered in the daily lives of the general population. On a related note, NBAC also recommended that each component of a study be evaluated separately, and its risks should be both reasonable in themselves as well as be justified by the potential benefits to society or the participants. Potential benefits from one component of a study should not be used to justify risks posed by a separate component of a study. This type of component analysis is not currently required by or mentioned in the Common Rule, which directs IRBs to weigh the risks and potential benefits of the entire study (*See* 45 CFR 46.111(a)(2)). In other words, the Common Rule allows an IRB to justify an increased risk posed by one portion of a research study, by a benefit gleaned from a separate portion of a research study, or by the entire study.[85]

The IOM investigated the issue of levels of review in *Responsible Research*. It recommended that the degree of scrutiny, the extent of continuing oversight, and the safety monitoring procedures for research proposals should be calibrated to a study's degree of risk. Specifically, IOM recommended that OHRP coordinate the development of guidance for risk stratification, and develop and disseminate best practices in order to lessen the extreme variability in the approval decisions and regulatory interpretations among IRBs.

IRB Shopping. A second potential issue concerns the local flexibility that the Common Rule and FDA regulations (and the HIPAA Privacy Rule, by cross reference to the Common Rule) give to IRBs in determining and weighing risks and benefits. The Common Rule and FDA regulations require an institution, or when appropriate an IRB, to prepare and maintain adequate documentation of IRB activities (45 CFR 46.115 (HHS); 21 CFR 56.115 (FDA)), but contain no requirement that a researcher, institution, or any other party inform an IRB if a study was previously disapproved by another IRB. The local flexibility that individual IRBs have may thus lead to "IRB shopping" — a situation in which sponsors and/or research investigators who are unhappy with one IRB's reviews switch to another without the new IRB being aware of the other's prior involvement.

Concerns about IRB shopping are twofold. First, there is the concern that the practice may deprive the new IRB of information that may be important for protecting human subjects. Second, there is the worry the practice might enable sponsors and clinical investigators to ignore rather than address the concerns raised by an unfavorable IRB review decision.[86] Some reports of IRB shopping were included in the OIG's 1998 report *Institutional Review Boards: A Time for Reform* (*Reform Report*), which stressed that seeking a second IRB's approval was

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[85] A form of component analysis was recommended by the SACHRP Research Involving Children Subcommittee (focused on research conducted under 45 CFR 46 Subpart D, which is not a part of the Common Rule). The subcommittee suggested that each research procedure in a treatment study be independently evaluated in terms of benefits and risks to subjects. The recommendation generated a great deal of discussion and no consensus at the April 2005 SACHRP meeting. [http://www.hhs.gov/ohrp/sachrp/], visited Apr. 20, 2005.

[86] FDA, *Institutional Review Boards: Requiring Sponsors and Investigators to Inform IRBs of Any Prior IRB Reviews*, Docket No. 01N-0322. (67 FR 10115, Mar. 6, 2002)

acceptable, but suggested that the second IRB should be informed about the actions of the first.

In response to the OIG report, in 2002 FDA issued an advance notice of proposed rulemaking (*Institutional Review Boards: Requiring Sponsors and Investigators to Inform IRBs of Any Prior IRB Reviews*, 67 Federal Register 10115) The proposed rule would require sponsors and investigators to inform IRBs about any prior IRB review decisions. Among other things, the notice called for comments, particularly on the question of how often IRB shopping actually occurs, and whether the proposed rule would be beneficial.

FDA received a range of responses. Some, such as the Applied Research Ethics National Association (ARENA), supported the requirements — stressing that FDA should make it incumbent on sponsors (not IRBs) to provide the information.[87] Others, such as the Biotechnology Industry Organization (BIO), wrote that because no evidence suggests that IRB shopping is a common occurrence, a reporting requirement would add an unnecessary administrative burden to IRBs.[88] Still others, such as the American Society of Gene Therapy (ASGT), suggested that, even if it is established that IRB shopping occurs, it may occur for benign reasons.[89] For example, while it may be that sponsors seek IRBs with less expertise or rigor in hopes that they will approve studies, the opposite may also be true — that IRBs inexperienced in certain areas may choose to disapprove trials which they are uncomfortable reviewing.

One additional group, the Association of American Medical Colleges (AAMC), pointed out that medical schools and teaching hospitals are not able to conduct research with human participants that has not been approved by their institutional IRB — so there is no incentive to IRB shop.[90] However, in multi-site trials (where

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[87] Letter from Daniel Nelson, President, ARENA President, et al., to FDA June 4, 2002, at [http://www.fda.gov/ohrms/dockets/dailys/02/Jun02/060702/01N-0322-EC-12.html], visited Apr. 11, 2005.

[88] Letter from Michael Werner, Vice President, Bioethics, BIO, to FDA, Apr. 6, 2002, at [http://www.fda.gov/ohrms/dockets/dailys/02/Jun02/060702/01N-0322-EC-11.html], visited Apr. 11, 2005.

[89] Letter from Malcolm Brenner, President of the ASGT, to FDA, May 24, 2002, at [http://www.asgt.org/regulatory_issues/nih_guidelines_compliance_recent_changes_response.html], visited Apr. 11, 2005.

[90] Letter from Jordan J. Cohen of the AAMC to FDA, April 8, 2002, at [http://www.aamc.org/advocacy/library/research/corres/2002/040802.htm], visited Apr. 11, 2005. Note that in April 2005, OHRP sent a letter to University of Washington (UW) in which findings of noncompliance relative to systemic protections for human subjects were listed. Letter from Karena Cooper, Compliance Oversight Coordinator, Division of Compliance Oversight, OHRP, to Mark A. Emmert, President, University of Washington, *Re: Human Research Subject Protections Under Federalwide Assurance FWA-6878* (Apr. 1, 2005). In response, UW's Vice Provost for Research, Craig Hogan, reportedly said, among other things, that IRB shopping will end. See Alexander Otto, "Feds Find More Cause for Concern with uw," *News Tribune* [Tacoma, WA], Apr. 20, 2005, p. A1.

multiple IRBs would be involved), AAMC favored the recommendation that sponsors disclose prior IRB judgments to other IRBs.

Proposed Legislation Affecting IRBs. Regarding the issue of IRB membership, H.R 3594 (108th Congress) contained provisions regarding racial diversity, scientific expertise, non-scientific expertise, and independence from the institution. On the topic of racial diversity, the bill would have expanded upon the Common Rule's general requirement that IRBs be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. The bill would have directed the HHS Secretary publish a determination of whether IRBs, when reviewing proposals for research in which the subjects are primarily minorities, include sufficient numbers of members from the same minority group. In addition, the Director of OHRP would have been able to make grants to recruit and train minority individuals to serve on IRBs. On the topic of the number of IRB members that must have scientific expertise, H.R. 3594 would have increased the Common Rule's requirement from at least one (of at least five members), to the greater of two members or 25 percent of all members. Similarly, the bill would have increased the Common Rule's requirements regarding the number of members who must have non-scientific expertise and the number who must be otherwise unaffiliated with the institution from at least one of each, to the greater of at two members or 20 percent of all members for each category. The bill would have expanded the rule on quorum for decision-making: quorum would not have been established — and thus the IRB could not have acted — unless one or more members from each of the above categories were present.

H.R. 3594 (108th Congress) would have addressed the topic of IRB registration, enhancing OHRP's requirement for IRB registration (implemented in 2000), by requiring IRBs to register with the HHS Secretary in a manner and form specified by the Secretary. The institution served by the IRB would have been required to submit annually to the Secretary a report that compiles data on the number of new research proposals reviewed, the number of continuing research projects reviewed, and the number of reviewed biomedical research proposals.

To facilitate the training of future IRB members, H.R. 3594 (108th Congress) would have required the institution served by the IRB to ensure that the Board had an orientation program for new members and a continuing education program for existing members of the Board. With respect to ethical matters that related to research, the bill would have required a continuing education program for all members of the Board. The Common Rule currently has no such requirement.

S. 3060 (107th Congress) would have addressed the topic of weighing risks and potential benefits by providing specific examples of the types of research considered

to have greater or less than minimal risk to subjects. The Common Rule itself does not contain examples.[91]

Mistakes and Misconduct

During the course of clinical research, mistakes and misconduct of researchers, IRBs, and /or institutions can lead to the injury of human subjects and to the introduction of ineffective drugs, devices, or biologics into the marketplace. In order to reduce mistakes and misconduct, recommendations have been made that rules governing conflicts of interest in research be strengthened; that accreditation be required for IRBs, researchers and institutions; that smoother protocols be implemented for reporting adverse events in multisite trials; and that better provisions be created to monitor ongoing research.

Conflicts of Interest Rules. Conflicts of interest are relationships and/or arrangements that may inappropriately influence the behavior of investigators, sponsors and/or IRB members, potentially putting human subjects at risk. Increasingly, there has been interest in avoiding and/or managing conflicts of interest in biomedical research, particularly those created by investigators' and reviewers' financial ties to institutions whose products are being investigated. The In 2004, Congress investigated federal agencies' awards, contracts, and agreements between employees and outside entities, and paid particular attention to the NIH.[92]

In February 2005, NIH responded to pressure from Congress and the public when it announced new, more stringent conflict of interest guidelines for its employees. The guidelines, which are not a part of 45 CFR 46 or the Common Rule, generally prohibit NIH employees (a category that does not include grant recipients, or employees of other agencies that have adopted the Common Rule) from accepting compensation from or engaging in a range of business dealings with pharmaceutical and biotechnology companies, supported research institutions, health care providers and insurers, and related trade, professional or similar associations.[93] One provision

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[91] Note that in 1998, OPRR published some categories of research that may be reviewed using an expedited procedure if the research also involves less than minimal risk. *Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure*, OHRP, (63 Federal Register 60364-60367 [Nov. 9, 1998], at [http://www.hhs.gov/ohrp/humansubjects/guidance/63fr60364.htm], visited May 3, 2005.

[92] See, e.g., House Committee on Energy and Commerce, Press Release*: Barton, Greenwood Ask 15 Federal Agencies to Disclose Awards, Contracts and Agreements Between Employees and Outside Entities*,, Jun. 18, 2004, at [http://energycommerce.house.gov/108/News/06182004_1322.htm], visited Apr. 11, 2005; As a result of the congressional investigation and what FDA "termed 'a comprehensive review' of more than 1800 previously approved requests from its employees to engage in 'outside activities,' the United States Food and Drug Administration (FDA) has expanded the number of scientists and officials required to file confidential financial disclosure forms." "FDA Expands Disclosure," *The Scientist*, Jun. 21, 2004, at [http://www.biomedcentral.com/news/20040621/01], visited Apr. 11, 2005.

[93] *Supplemental Standards of Ethical Conduct and Financial Disclosure Requirements for* (continued...)

of the guidelines has caused some controversy and has reportedly led to difficulty hiring and maintaining top scientists at NIH.[94] The provision, which requires NIH employees who file public and confidential financial disclosure forms to divest stock and financial holdings in biomedical companies, and all other employees to have a maximum of $15,000 in investments, may be reevaluated.[95] NIH's entire conflicts of interest policy is open to public comment for one year before becoming final.

Another NIH policy, revised in January 2005, articulates restrictions for grant reviewers that are similar to the new restrictions governing NIH employees (at [http://grants.nih.gov/grants/peer/COI_Information.pdf]). HHS took action as well, creating a guidance document to assist IRBs, researchers and institutions with conflicts of interest related to human subjects research,[96] proposing enhancements to the conflicts rules for applicants and recipients of its funding,[97] and calling for research proposals to foster integrity in research.[98]

By contrast to NIH, FDA, which already had a rigorous conflict of interest policy in place for its employees (a category that does not include persons applying to FDA for product approval), has not proposed recent changes to its policy. The policy generally prohibits not only FDA employees but also their spouses and minor children from having financial interest in a significantly regulated organization, such as a drug company for example. The policy has some exceptions, and also allows for the possibility of obtaining a waiver in certain circumstances.[99] (5 CFR 5501.104) For an investigator submitting clinical trial data to support an application to market a product, FDA requires the disclosure or certification information concerning his or her financial interests if he or she is not an employee of the product's sponsor. (21 CFR 54)

While much of the recent publicity regarding conflicts of interest has been focused on grant-makers' and researchers' financial, institutional and professional

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[93] (...continued)
Employees of the Department of Health and Human Services, RIN 3209-AA15, 70 Federal Register 5543, Feb. 3, 2005.

[94] Andrew J. Hawkins, "NIH Stock Divestitures May Have to Be Rethought, Zerhouni Says", *Washington FAX*, Apr. 7, 2005.

[95] Ibid.

[96] Tommy G. Thompson, HHS Secretary, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," *HHS Final Guidance Document*, May 5, 2004, at [http://www.hhs.gov/ohrp/humansubjects/finreltn/fguid.pdf], visited Apr. 7, 2005.

[97] Department of Health and Human Services, "Public Health Service Policies on Research Misconduct; Proposed Rule," 69 Federal Register 20777, Apr. 16, 2004.

[98] "Grant Program Initiated Aimed at Understanding Factors That Influence Research Integrity," *Washington Fax,* Aug. 13, 2004.

[99] In addition, FDA's Commissioner has a permanent five-member Conflict of Interest Review Board that is to review and make recommendations on all specific or policy matters relating to certain conflicts of interest arising within the FDA (21 CFR 19.10).

potential biases,[100] some similar issues have been raised regarding IRB members' potential conflicts of interest. The Common Rule and FDA regulations governing IRB conflicts are identical and preclude any member from participating in reviews with regard to which the member has conflicting interest, except to provide information requested by the IRB (45 CFR 46.107(e)(HHS); 21 CFR 56.107(e)(FDA)). Similarly, the HIPAA Privacy Rule prohibits privacy boards from having any members participating in a review of any project in which the member has a conflict of interest (45 CFR 45 CFR 164.512(i)(1)(i)). None of the regulations overtly govern conflicts of interest that researchers or institutions may have, although the Common Rule and FDA regulations to require an investigator to seek informed consent only under circumstances that minimize the possibility of coercion or undue influence, which may be interpreted to preclude such conflict (45 CFR 46.116).[101] None of the regulations specify what constitutes a conflict.

In *Responsible Research*, the IOM recommended that conflicts of interest reviews for researchers and IRBs be conducted by a distinct body other than the IRB prior to ethical review. NBAC also addressed the topic, recommending in *Human Participants* that Federal policy define institutional, IRB, and investigator conflicts of interest, and issue guidance to ensure that the rights and welfare of research participants are protected. NBAC also recommended that all relevant conflicts of interest be disclosed to participants.

Accreditation of IRBs, Researchers and Institutions. Accreditation is a procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks. Accreditation may be used in conjunction with, but is distinct from, both certification (a procedure by which a disinterested party gives written assurance that a product, process, individual, or service conforms to specified requirements) and or registration (a procedure by which a body indicates relevant characteristics of a product, process or service, or particulars of a body or person, in an appropriate publicly available list). Neither the Common Rule nor FDA regulations require the accreditation of IRBs, researchers, or institutions to conduct human subjects research. Likewise, the HIPAA Privacy Rule does not require accreditation of its privacy boards.

Though it does not require accreditation, the Common Rule does require each institution it funds to provide to the governing federal agency a written assurance that

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[100] *See, e.g.*, Michelle Mello, *et al.*, "Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry," *The New England Journal of Medicine*, vol. 351, no. 21, p. 2202 (May 26, 2005).

[101] E.g., "Financial interests are not prohibited, and not all financial interests cause conflicts of interest or affect the rights and welfare of human subjects. HHS recognizes the complexity of the relationships between government, academia, industry and others, and recognizes that these relationships often legitimately include financial relationships. However, to the extent financial interests may affect the rights and welfare of human subjects in research, IRBs, institutions, and investigators need to consider what actions regarding financial interests may be necessary to protect those subjects." Tommy G. Thompson, Secretary, HHS, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection" *Financial Guidance Document* (May 5, 2004), at [http://www.hhs.gov/ohrp/humansubjects/finreltn/fguid.pdf].

it is complying with the regulations, including those pertaining to the membership and review procedures of IRBs (45 CFR 46.103(a)). OHRP is to review the assurances made to HHS (but not to FDA) and determine if the institution is in compliance. Rarely, OHRP will inspect a facility. FDA may send inspectors to check on IRBs to ensure compliance with its human subjects regulations during clinical trials, and has provisions for disqualifying an IRB from participation in continued or additional research if the IRB fails to meet the regulatory requirements.

Neither the Common Rule nor FDA regulations require the accreditation of investigators, but if a federal funding agency or the FDA learns that an investigator is failing to follow human subjects protection requirements (such as those contained in the Common Rule) the investigator's federal funding or FDA application may be terminated. As is the case for compliance with IRB regulations, the Common Rule requires institutional assurances of compliance with investigator regulations. OHRP is to review the assurances and may inspect facilities. Likewise, FDA may also inspect facilities to ensure compliance.

For investigators, both the Common Rule and FDA regulations require them to maintain and report to IRBs specific types of documentation related to the protection of human subjects. The HIPAA Privacy Rule requires the same with respect to its privacy boards. In addition, since October 2000, NIH has required that all investigators submitting NIH applications for research grants involving human subjects be educated about human subjects protection (at [http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html]). This education requirement means that researchers will have successfully completed a short course. It does not mean that their processes for human subjects protections have been reviewed and accredited.

Several groups have made recommendations for accreditation of institutions that conduct human subjects research, investigators, and IRBs. In 2000, following an April 1999 announcement from the Under Secretary for Health of the Veterans Health Administration (VHA), the VHA engaged an external contractor, the National Committee for Quality Assurance (NCQA),[102] to inspect and certify the human subjects protection program of every VA facility conducting research involving human subjects (Veterans Affairs Medical Centers - VAMCs).[103] In 2001, NCQA and VHA launched the first ever accreditation program for human research

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[102] NCQA is an independent, 501(c)(3) non-profit organization whose mission is to improve health care quality everywhere. Information about its *VA Human Research Protection Accreditation Program (VAHRPAP)* can be found at [http://www.ncqa.org/Programs/QSG/VAHRPAP/vahrpap.htm], visited May 3, 2005.

[103] Testimony of Thomas L. Garthwaite, M.D,, Under Secretary for Health, Department of Veterans Affairs, on the *Protection of Human Subjects of Research in the Veterans Health Administration*, before the Subcommittee on Oversight and Investigations of the Committee on Veterans' Affairs, U.S. House of Representatives (Sept. 28, 2000), at [http://veterans.house.gov/hearings/schedule106/sept00/9-28-00/tgarthwa.htm], visited May 3, 2005.

protection.[104] NCQA reportedly conducted accreditation visits to 23 facilities — 20 of which were accredited with conditions,[105] two of which were not accredited, and one of which withdrew from the process.[106] As of May 1, 2005, NCQA had listed as accredited 38 of the 45 VAMCs which have so far attained any form of NCQA accreditation status.[107] According to the VA's Office of Research Oversight, approximately 117 VAMCs conduct human subjects research.[108] The VA reportedly expects accreditation of all VAMC facilities to be completed by the summer of 2005.[109]

In 2001, the IOM and the NBAC each recommended implementing an accreditation program for research institutions as one possible tool for strengthening the current system.[110] In 2002, IOM recommended in *Responsible Research* that, in addition, research sponsors develop criteria for evaluating the performance and enhancing the practice of quality improvement, and that institutions have written policies and procedures that detail internal auditing and oversight processes. Some in industry oppose measures like accreditation that might increase the cost of research.[111] Others claim that the resulting good practice and proper conduct in

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[104] "NCQA, VA Launch First Ever Accreditation Program for Human Research Protection," *NCQA News*, (Aug. 28, 2001), at [http://www.ncqa.org/communications/news/vahrpaplaunch.htm], visited May 3, 2005.

[105] "A facility accredited with conditions met most of the accreditation standards."Testimony of Cynthia A. Bascetta, Director, Health Care, Veteran's Health Benefits Issues, on *VA Research: Actions Insufficient to Further Strengthen Human Subjects Protections* before the Subcommittee on Oversight and Investigations, Committee on Veteran's Affairs, House of Representatives (Jun. 18, 2003), at [http://veterans.house.gov/hearings/schedule108/jun03/6-18-03/cbascetta.pdf].

[106] Ibid.

[107] "Veteran's Affairs Human Research Protection Accreditation Program Status List," *NCQA*, (May 1, 2005), at [http://www.ncqa.org/Programs/QSG/VAHRPAP/VA%20Status%20List.pdf], visited May 5, 2005.

[108] Telephone conversation with Peter N. Poon, JD, MA, Health Science Specialist, Office of Research Oversight, VA (202) 565-8107, on May 9, 2005.

[109] Testimony of Cynthia A. Bascetta, Director, Health Care, Veteran's Health Benefits Issues, on *VA Research: Actions Insufficient to Further Strengthen Human Subjects Protections* before the Subcommittee on Oversight and Investigations, Committee on Veteran's Affairs, House of Representatives (Jun. 18, 2003), at [http://veterans.house.gov/hearings/schedule108/jun03/6-18-03/cbascetta.pdf].

[110] IOM, *Preserving Public Trust: Accreditation and Human Research Participant Protection Programs* (Washington, DC: National Academy Press, Apr. 2001); NBAC, *Ethical and Policy Issues in Research Involving Human Participants*, Aug. 2001, p. 11.

[111] According to the 2005 fee schedule for the *Association for the Accreditation of Human Research Protection Programs, Inc.* (an organization that accredits IRBs and institutions) the cost of accreditation varies with the number of protocols it reviews annually, rising as the number of protocols increases. For example, for an IRB or an institution with an IRB that reviews less than 100 protocols per year, the application fee is $8,100 and the annual fee is $4,400 thereafter. For 2,501-3,000 protocols per year, the application fee is $26,600,

(continued...)

research would pay off both scientifically and economically; the problems that flow from poorly conducted human subjects research may call results into question, and may cause harm to the subjects, leading to medical expenses and possibly to litigation and a loss of investor confidence.[112]

The Secretary's Advisory Committee on Human Research Protections (SACHRP) has recommended voluntary accreditation of IRBs. Two programs provide voluntary accreditation for IRBs and for institutions involved in human subjects research: the Partnership for Human Research Protection, Inc. (PHRP - which was formed by NCQA) and the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP). According to the AAHRPP and PHRP websites, as of May 3, 2005, a combined total of 19 institutions and 6 IRBs had been accredited, and two institutions had received a qualified accreditation.[113] AAHRPP and PHRP keep the accreditation process confidential, so the number of accreditation applicants is not published.[114] SACHRP expressed concern that the cost and scope of the accreditation process may be impediments for some institutions to seek accreditation. They also believe, however, that natural market pressures would push institutions toward seeking accreditation.[115]

Adverse Event Reporting and Multisite Research. An *adverse event* (AE) is an unfavorable medical occurrence in subjects exposed to drugs, biologics, or medical devices. For example, an AE may be nausea, dry mouth, anxiety, or even death. *Adverse event reporting* (AER) is the process of disseminating information about individual AEs to the principal investigators and IRBs, and where appropriate, to regulatory agencies and consumers. In the event that the principal investigator determines that an AE constitutes a new or previously unidentified risk, the informed

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[111] (...continued)
and the annual fee is $11,000 thereafter. "Fees," Association for the Accreditation of Human Research Protection Programs, Inc., at [http://www.aahrpp.org/www.aspx?PageID=17], visited Apr. 11, 2005.

[112] William Alexander, et al., "Realities at the leading edge of research," *EMBO Reports*, vol. 5, no. 4 (2004), p. 324.

[113] Note that both AAHRPP and PHRP list a review of an institution's IRB as one component of institutional accreditation. AAHRPP lists 14 organizations and four IRBs that they have accredited, and two organizations with qualified accreditation. PHRP lists five organizations and three IRBs they have accredited. One IRB (Chesapeake Research Review, Inc.) is accredited by both organizations. [http://www.aahrpp.org/www.aspx?PageID=11$1$100]; [http://www.phrp.org/show.asp?durki=6856], both visited May 3, 2005.

[114] "Because the accreditation process is confidential, AAHRPP does not release information about applicants that are in the process of seeking accreditation or those that have been placed in the Accreditation-Pending or Accreditation Withheld categories." Accredited Organizations, *AAHRPP*, at [http://www.aahrpp.org/www.aspx?PageID=11$1$100], visited May 3, 2005. *See also*, "Confidential Information" in *Public Policy Information*, *PHRP*, at [http://www.phrp.org/show.asp?durki=6720&site=54&return=4819], visited May 3, 2005.

[115] Felix A. Khin-Maung-Gyi, "Final Accreditation Subcommittee Report" *Presentation to SACHRP*, Alexandria, VA, March 29, 2004, at [http://www.hhs.gov/ohrp/sachrp/mtgings/mtg03-04/accredrpt_files/frame.htm], visited Apr. 11, 2005.

consent form may need to be revised to reflect the new risk. Any consent revisions must be submitted to the IRB along with the adverse event information. If the IRB determines there is an increased risk to subjects based on the adverse event reports, the research may be suspended.

Both HHS's Common Rule and the FDA's regulations have provisions that apply to AER. (HIPAA's Privacy Rule, which is focused on protecting information rather than patient safety, contains no provisions regarding AEs or AER, except by reference to FDA regulations (45 CFR 164.512(b)(1)(iii)(A)). The Common Rule requires institutions that receive federal funding to assure their funders that they have written procedures for AER. Procedures must require reporting to the IRB, appropriate institutional officials, and the department or agency head of any *unanticipated* problems involving risks to subjects (45 C.F.R. 46.103(b)(5)). The Common Rule does not specify who is or should be made responsible for reporting this information to the IRB. The FDA has parallel (although not identical) requirements. (21 CFR 56.108(b)).[116]

Recent public discussions regarding problems with AER requirements have focused the interaction of the Common Rule's requirements with a separate set of FDA regulations — those governing *Investigational New Drug Applications* (INDs), which sponsors submit to obtain FDA permission for clinical trials to test new drugs. FDA's IND regulations require a researcher to inform the sponsor if a drug effect is *adverse* (21 CFR 312.64(b)), and to the IRB if a problem involving risk to human subjects is *unanticipated* (21 CFR 312.66). Alone, these regulations may be in harmony with the Common Rule. However, the IND regulations also require the sponsor to notify FDA and all participating investigators of an adverse experience associated with the use of the drug if it is both *serious and unexpected* (21 CFR 312.32(c)(1)(i)(A)). When applied to multicenter trials (in which multiple investigators and IRBs may be involved), this *serious and unexpected* threshold, when contrasted with the Common Rule's *unanticipated* threshold has caused confusion for investigators, sponsors, and IRBs in two points. First, when an unanticipated but not serious AE occurs at one research site, must all of the IRBs in the study — or perhaps one centralized IRB — be informed, and by whom? Second, who is responsible for determining whether an AE is serious — a researcher, sponsor, or IRB?

Questions that do not focus on the differences between the Common Rule's and FDA's regulatory requirements have also been raised. Even if dealing with a single set of regulations, the AER process has been described as unwieldy for some research conducted at multiple locations, and therefore with many investigators and IRBs. The Common Rule specifies that, in multi-site research, each institution is responsible for safeguarding the rights and welfare of human subjects at its location, though the Rule does provide that a Department or Agency head may approve a joint review arrangement that allows one IRB to rely upon the review of another qualified

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[116] The one distinction between the Common Rule at 46.103(b) and the FDA regulations at 56.108(b) is that FDA requires IRBs to follow written procedures for reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration, where the Common Rule requires reporting to the department or agency head.

IRB to avoid duplication of effort (45 CFR 46.114). By contrast, FDA regulations allow for joint review without requiring approval from a Department or Agency head (21 CFR 56.114).[117] Given that each institution is responsible for protecting subjects at its location, it may make sense for all AERs to be shared among all relevant personnel and IRBs. On the other hand, the IRB of a major research institution with scores of researchers, each playing large and small roles in multiple protocols, may be inundated with AERs, many of which may not be relevant to the portion of the research being conducted at the IRBs's location.[118]

In March 2005, the FDA issued a draft *Guidance for Industry — Using a Centralized IRB Process in Multicenter Clinical Trials*,[119] which was preceded by a public meeting to discuss AER during multi-site trials.[120] Some groups suggested that it would help IRBs to manage their workload if sponsors and investigators were able to decide which AEs merited reporting to the IRB.[121] Others criticized the suggestion, stressing that the primary purpose of IRBs is to protect research subjects and recommending that measures be taken to further insure independence of IRBs from both sponsors and parent institutions who may have conflicts of interest with regard to determining what constitutes an AE.[122]

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[117] In Mar., 2005, FDA made available for comment a draft guidance document to assist sponsors, institutions, institutional review boards (IRBs), and clinical investigators involved in multicenter clinical research in meeting the requirements of 21 CFR part 56 by facilitating the use of a centralized IRB review process: *Using a Centralized IRB Review Process in Multicenter Clinical Trials*, Mar. 2005 at [http://www.fda.gov/cder/guidance/OC273.htm], visited May 3, 2005.

[118] For example, one major research center (Washington University in St. Louis, MO) had over 11,000 AERs delivered to its IRB in 2003. Patricia Scannell, "Using Technology to Strengthen Human Subject Protections," presented at the Fourth National Medical Research Summit, Baltimore, MD, Apr. 2004.

[119] Available from FDA at [http://www.fda.gov/cder/guidance/OC273.htm], visited May 3, 2005.

[120] FDA, HHS, "Reporting of Adverse Events to Institutional Review Boards; Public Hearing" *Public Hearing Notice* [Docket No. 2005N — 0038], 70 Federal Register 6693 (Feb. 8, 2005).

[121] See, e.g., Yvonne K. Higgins, Associate Director, Office of Regulatory Affairs, University of Pennsylvania, "PENN's Response to Managing Adverse Event Reports," presentation at *FDA's public meeting on Reporting of Adverse Events to Institutional Review Boards*, March 21, 2005. The most recent comments on FDA's meeting can be found on the FDA Dockets website [Docket number 2005N-0038] at [http://www.fda.gov/ohrms/dockets/dockets/05n0038/mostrecent.htm], visited Apr. 11, 2005.

[122] See, e.g., "Statement of Michael Susko," President, Citizens for Responsible Care and Research, presented to FDA's *Reporting of Adverse Events to Institutional Review Boards*, March 21, 2005. The most recent comments on FDA's meeting can be found on the FDA Dockets website (Docket number 2005N-0038) at [http://www.fda.gov/ohrms/dockets/dockets/05n0038/mostrecent.htm], visited Apr. 7, 2005.

SACHRP has begun to address the issues faced by IRBs in the AER process. It has received reports that IRBs have experienced some of the following difficulties:[123]

- applying nonuniform FDA and HHS requirements together;
- discerning whether, in multi-site drug trials, IRBs must share AERs with all of the sites' IRBs if modification at only one center is needed;
- determining which AEs are "expected" (and thus carry no multi-center reporting requirement according to FDA regulations); and
- handling the workload generated when all IRBs in a multi-site trial report all AEs (no matter how small) to all other IRBs involved.

In March 2004, SACHRP voted to write to HHS Secretary Thompson asking that FDA and ORHP "promptly issue official guidance that is clear and consistent guidance on IRB review of both internal and external AERs which will best serve to protect human subjects and effectively reduce regulatory burden."[124] The discussion leading to the vote was reflective of some differences of opinion regarding whether reform for AER is necessary or desirable. Some expressed favor for easing the reporting burdens on IRBs, harmonizing HHS and FDA AER guidelines, as well as a streamlining of the reporting process. Others said they would like to keep IRBs more intensively involved in the review of AERs, both to protect subjects and to minimize liability. In any case, most agreed that HHS and FDA should produce guidance documents and/or training for IRBs on the existing requirements.

NBAC addressed AERs in *Human Participants*, recommending that the federal government create a uniform system for reporting and evaluating adverse events occurring in research, especially in multi-site research, clarifying the reporting and evaluation responsibilities of investigators, sponsors, IRBs, Data and Safety Monitoring Boards,[125] and federal agencies. NBAC further recommended that for multi-site research, federal policy should permit central or lead IRB review, rather than the common practice of review by multiple IRBs at multiple sites.

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[123] Ernest P. Prentice, "IRB Review of External Adverse Event Reports (AERs)," *presentation at SACHRP meeting*, Alexandria, VA, Mar. 2004, at [http://www.hhs.gov/ohrp/sachrp/mtgings/mtg03-04/discissues_files/frame.htm], visited Apr. 11, 2005.

[124] *See* SACHRP Meeting Minutes, March 29-30, 2004, at [http://www.hhs.gov/ohrp/sachrp/mtgings/mtg03-04/min0330.html], visited Apr. 21, 2005.

[125] A Data and Safety Monitoring Board (DSMB) is an entity distinct from an IRB that conducts and reports to the sponsor the results of (1) reviews of accumulating clinical data relating to the efficacy and safety of the investigational product (drug, biologic and/or device); (2) interim analyses of the clinical data to determine whether the study needs to be terminated for safety reasons; and (3) evaluations of the continued scientific validity and merit of the study. DSMB review is required by some federal sponsors for some research See, e.g., "NIH Policy for Data and Safety Monitoring," June 10, 1998, at [http://grants.nih.gov/grants/guide/notice-files/not98-084.html], visited Apr. 11, 2005.

IOM looked more broadly at issues involved with multicenter trials in its report, *Responsible Research*. It recommended that research organizations, sponsors, and IRBs streamline the reviews and processes in multisite trials by assigning a lead review committee for each trial. This assignment could resolve issues involved with AER as well as those related to the lack of consistency in the levels of review among various IRBs.

Informed Consent. While it is generally accepted that meaningful informed consent is an essential component of human subjects protections, some questions have been raised regarding whether the informed consent requirements of the Common Rule (and the identical FDA informed consent requirements)[126] could be improved.[127] For example, the Common Rule's emphasis on informed consent documentation has sparked some inquiry into whether the Rule's requirements — that a person read and sign a form — actually result in subjects' understanding the research so that they can meaningfully agree to participate. Some investigators have found that tools such as documents tailored to low-level readers, culturally appropriate visual aids, and interactive process are helpful in ensuring that potential subjects not only receive, but also understand the information that they need in order to decide whether to participate in a research study.[128]

In order to ensure that consent is achieved and documented, IOM recommended in *Responsible Research*, that the informed consent process consist of a dynamic, ongoing, interactive dialogue between staff and research participants. To distinguish the legal documentation from the interactive process, the IOM recommended that forms signed to provide legally valid consent be called *consent forms* rather than *informed consent forms*. IOM stressed that IRBs should ensure that the focus of the informed consent process and the consent form is on informing and protecting participants, NOT on protecting institutions. Further, the protection program should be transparent and open to the public.

The NBAC made similar recommendations in *Human Participants*, suggesting that Federal policy emphasize the process of informed consent rather than the documentation and ensure that competent participants have given their voluntary informed consent. NBAC also recommended issuing guidance about how to provide information to prospective subjects, how to promote their comprehension, and how to ensure that they continue to make informed and voluntary decisions.

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[126] The content of 45 CFR 46.116 (the Common Rule's informed consent requirements) is identical to 21 CFR 50.25 (the FDA regulation's informed consent requirements).

[127] The HIPAA Privacy Rule does not require informed consent, but rather requires researchers to obtain an *authorization* from those whose information is used. (For more information about the authorization process and its interaction with informed consent, see the HIPAA Privacy Rule section in **Appendix A** of this report.)

[128] See, e.g., D. R. Young, D.T. Hooker, and F.E. Freeberg. "Informed Consent Documents: Increasing Comprehension by Reducing Reading Level." *IRB: A Review of Human Subjects Research* vol. 12, no. 3, 1990; NBAC, *Ethical and Policy Issues in Research Involving Human Participants*, Aug. 2001, p. 100.

Monitoring of Ongoing Research. While much of the focus of the federal human subjects protection regulations falls on review prior to the start of research, some provisions also deal with the appropriate way to monitor ongoing research. The Common Rule and FDA regulations each require IRBs to have written procedures that specify how they will conduct continuing review of ongoing research. (The HIPAA Privacy Rule has no parallel provision.) The reviews should be conducted at intervals appropriate to the degree of risk, but not less than once per year (45 CFR 46.103(b)(4), 109(e) (HHS); 21 CFR 56.109(f) (FDA)). However, other than granting IRBs the authority to observe (or have a third party observe) the consent process and the research, the regulations do not specify how the ongoing review should occur.

In *Human Participants*, NBAC found that continual review and oversight of ongoing research are necessary to ensure that emerging data or evidence have not altered the risks/potential benefits assessment to make the risks no longer reasonable. Therefore, NBAC recommended that federal policy be developed to describe how sponsors, institutions, IRBs and investigators should monitor ongoing research. NBAC advised that continuing review was not necessary for studies involving minimal risk, research involving the use of existing data, or research that is in the data analysis phase when there is no additional contact with participants. However, when continuing review was not required, NBAC recommended that other mechanisms be in place for ensuring the compliance of investigators and for reporting protocol changes or unanticipated problems encountered in the research.

Proposed Legislation Affecting the Prevention of Mistakes and Misconduct. On the topic of adverse event reporting, H.R. 870 (109th Congress) would create criminal penalties for drug manufacturers' chief executives and/or other members of the senior executive management group who knowingly conceal reports of serious adverse drug experiences related to drugs for which the manufacturer was seeking or had received FDA approval for marketing. An executive found to have violated the Act would incur fines of not more than $2,000,000, a prison term of a minimum of 20 years to life, or both. The Act would also prohibit a company from indemnifying any person found to have violated its provisions.

On the topic of conflicts of interest, H.R. 3594 (108th Congress) would have required the HHS Secretary to review the Common Rule and other applicable regulations not later than 18 months after the enactment of the Act addressing (among other things) issues related to significant financial interest, and attestations by clinical investigators regarding the protection of human subjects. In addition, H.R. 3594 would have required IRB members to disclose significant financial interests, and to have recused themselves from reviewing proposals in which they had a significant conflict or interest. Investigators would have been required to disclose to IRBs any significant conflicts of interest related to the research, any previous disqualifications or restrictions by any Federal entity in their ability to conduct human subject research, and any previous IRB reviews. The institution served by the IRB would have also had to review the potential investigators' conflicts of interest, and have sought to manage, reduce, or eliminate such conflicts.

On the topic of IRB accreditation, H.R. 3594 (108th Congress) would have given the HHS Secretary the authority to recognize a private accrediting entity or entities, and to facilitate but not to require IRB accreditation.

For research projects involving multiple locations, H.R. 3594 (108th Congress) would have enabled the requirements of the Common Rule to be met by a single lead IRB. A principal investigator would have had to report AEs to the lead IRB (not necessarily to all IRBs) and the sponsor, in a timely manner appropriate to the severity and unexpectedness of the event.

On the topic of monitoring ongoing research, H.R. 3594 (108th Congress) would have enabled IRBs to report regulatory non-compliance to the HHS Secretary. The bill would have also required the Director of OHRP to provide advice to institutions regarding compliance with the Common Rule and improvements in human subjects protections. The Director would have been able to conduct audits to ensure compliance with the Common Rule, and offer corrective action and/or impose restrictions.

S. 3060 (107th Congress) would have required that all IRBs be accredited by the Director of ORHP within six years. The basis for accreditation would have been evaluated in terms of: the expertise of the members, adequacy of the members' education on principles and procedures of human research participant protections, whether decisions were insulated from financial conflicts of interest, whether research was reviewed in accordance with ethical principles, the informed consent process and the presence of research monitoring practices.

With regard to financial conflicts of interest, S. 3060 (107th Congress) would have required disclosure of potential conflicts of investigators and IRB members to the IRB or a conflict of interest committee. If the IRB granted a waiver for an investigator with such conflicts to participate in research, the investigator would have had to disclose the financial interest to participants in the research as part of the informed consent process. If a waiver was granted, the IRB could have required additional safeguards, including audits of the informed consent process, third party monitoring of the consent process, establishment of a data and safety monitoring board, requiring the investigator to hold financial interests in escrow prior to conducting the research or other measures as the IRB determined reasonable and necessary to protect participants. In addition, S. 3060 would have required investigators and sponsors to disclose any financial conflicts of interest to editors and publishers of peer-reviewed publications or other media.

Although S. 3060 (107th Congress) would have imposed no new informed consent requirements, it did have provisions for the Director to promulgate regulations regarding payment for recruiting or participation of the human subjects. S. 3060 also would have required the Director to promulgate regulations regarding the appropriate use of placebo or non-treatment in clinical studies.

Injuries and Medical Care

As a result of their participation in clinical research human subjects may sustain injuries, and may require routine and/or emergency medical care. The Common

Rule and FDA regulations (and the HIPAA Privacy Rule by reference) require that the informed consent document contain an explanation of any additional costs that the subject may incur as a result from participation in the research (45 CFR 46.116(b)(3) (HHS); 21 CFR 50.25(b)(3) (FDA). They also require that, for research involving more than minimal risk, the informed consent document must contain an explanation as to whether any compensation and medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained (45 CFR 46.116(a)(6)(HHS); 21 CFR 50.25(a)(6)). However, neither the Common Rule nor the FDA regulations specify if or when it is appropriate for IRBs, sponsors, or investigators to compensate subjects for the cost of their additional medical care or for research-related injuries.[129]

The Common Rule and FDA regulations also prohibit the inclusion of exculpatory language (through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence) in the informed consent document (45 CFR 46.116 (HHS); 21 CFR 50.20 (FDA)). This prohibition may suggest that such liability could flow from research. However, neither the Common Rule nor the FDA regulations prohibit sponsors, investigators, or others from asking subjects to sign documents that are unrelated to informed consent and contain exculpatory language.

Questions have been raised regarding who should bear the cost of subjects' medical care, and whether IRBs should be held legally liable for allowing a study that harmed a subject to take place. The following sections describe the debate and proposed legislation on these topics. There is no *proposed legislation* section at the end of the *injuries and medical care* section because legislation introduced in recent Congresses related to the Common Rule and protection of human research subjects would not have affected changes in this area; however relevant changes to Medicare and Medicaid laws are discussed in the *cost of medical care* section that follows.

Cost of Medical Care During Human Subjects Research and Compensation for Research-Related Injuries. When a person participates in research, the cost of tests, procedures, drugs and any research activity directly associated with the investigation, are typically covered by the group sponsoring the research, such as a pharmaceutical company or the NIH. On the other hand, the cost of routine patient care, which would typically be covered by the individual's health insurance plan if he or she were not enrolled in a study, may not be covered by the sponsor. These costs may also be excluded from insurance coverage, because some insurance providers define research and the related required medical services as *investigational* or *experimental*. Study participants may thus incur out-of-pocket

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[129] Since 1998, the Department of Veterans Affairs has required VA medical facilities to provide necessary medical treatment to research subjects injured as a result of participation in research projects approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees. (38 CFR 17.85, published at 63 Federal Register 11123 [Mar. 6, 1998])

costs for services such as such as the doctor visits, hospital stays, diagnostic tests and x-rays, that they would normally receive if not enrolled in a trial.[130]

In 2000, Medicare began covering the patient care costs of beneficiaries in some clinical trials.[131] While many state Medicaid programs have no legal requirements to cover clinical trials costs, many do cover all or some of the costs. In addition, a growing number of states have passed legislation or instituted special agreements requiring health plans to pay the cost of the routine medical care a patient receives as a participant in a clinical trial.[132]

IRB Liability for Research-Related Injury. In the course of human subjects research, IRBs are responsible for reviewing protocols, in part to assure that proper informed consent is obtained and that the human subjects are properly protected. In certain circumstances, persons harmed during research studies have sought to sue IRBs, in addition to investigators and sponsors. SACHRP heard a report about the current legal trends, potential sources of legal immunity for IRBs, and touched on the issue of whether subjects should be allowed to sue IRBs.[133] Proponents of litigation stressed the following:

- the tort system presents a good way to punish harm doers, or those who are negligent in their responsibilities;
- the threat of litigation motivates IRBs to adhere to best practices; and
- litigation itself gives people who suffer harms as a result of their participation in research a venue to hold accountable those

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[130] National Conference of State Legislatures (NCSL), "Clinical Trials: What Are States Doing? 2004 Update," 2003, at [http://www.ncsl.org/programs/health/2004clinicaltrials.htm], visited Apr. 12, 2005.

[131] "On Jun. 7, 2000, the President issued an executive memorandum directing the Centers for Medicare & Medicaid Services (CMS) to "explicitly authorize [Medicare] payment for routine patient care costs...and costs due to medical complications associated with participation in clinical trials." In keeping with the President's directive, this National Coverage Decision (NCD) serves to define the routine costs of clinical trials and identify the clinical trials for which payment for such routine costs should be made for eligible services furnished on or after Sept. 19, 2000. Centers for Medicare and Medicaid Services, *Medical Coverage — Clinical Trials, Provider Bulletin*, at [http://www.cms.hhs.gov/coverage/8d4.asp], visited Apr. 11, 2005.

[132] The following states have passed legislation requiring some degree of medical coverage for those who participate in certain clinical trials: Arizona, California, Connecticut, Delaware, Georgia, Illinois, Louisiana, Maryland, Maine, Massachusetts, Missouri, New Hampshire, Nevada, New Mexico, North Carolina, Rhode Island, Vermont, Virginia, and West Virginia. The following states have special agreements with insurance companies to voluntarily provide coverage for clinical trials; Georgia, Michigan, New Jersey, and Ohio. NCSL, *Clinical Trials: What Are States Doing?* 2004 Udpate, 2003, at [http://www.ncsl.org/programs/health/2004clinicaltrials.htm], visited Apr. 11, 2005.

[133] E. Haavi Morreim, "Litigation in Clinical Research: Problems and Solutions," *presented to SACHRP*, Alexandria, VA, April 2004 at [http://www.hhs.gov/ohrp/sachrp/mtgings/mtg03-04/morriem_files/frame.htm], visited Apr. 11, 2005.

responsible for ensuring an appropriate balance of risks and benefits and an appropriate informed consent process.

Opponents of litigation noted that obtaining information about litigation trends was difficult because of the lack of a centralized information source and a tendency of parties to settle rather than litigate. However, they expressed some concern that litigation, or the fear of it, might have the following effects:

- increased difficulty finding people to serve on IRBs (IRB members are generally unpaid);
- longer, more complex informed consent forms (informed consent forms may not contain exculpatory language, and they may create liability if they do not communicate the risks appropriately);
- unwieldy levels of adverse event reporting (discussed below) and other documentation;
- inhibition of research;
- increased cost of research for sponsors, including government, via higher indirect costs to cover liability insurance; and
- difficulty obtaining institutional and independent insurance.

SACHRP recommended that the report be transmitted to the IOM, and that no further action be taken on the subject.

NBAC looked into the issue of research-related injuries, recommending in *Human Participants* that the federal government study the issue to determine if there is a need for a compensation program. As an alternative to litigation related to research, IOM's *Responsible Research* contained the recommendation that a no-fault compensation system be set up to compensate any research participant who is injured as a direct result of participating in research, without regard to fault. Compensation should include at least the costs of medical care and rehabilitation. Rather than focusing on litigation against IRBs, IOM's proposals focused on compensating subjects for physical harm and avoiding litigation against sponsors and investigators. This may also eliminate the need for lawsuits against IRBs by compensating subjects without requiring that they prove others' wrongdoing.

The Future of Human Subjects Research Protections

The Common Rule does not contain language regarding how the system of human research protections can be reassessed, modified, or funded. Nevertheless, continued experience with human subjects regulations and the changing scope of the research protocols themselves can spark insights that may improve the regulatory system. Questions have arisen regarding whether there is a need to reassess the system periodically, what resources may be necessary to ensure the efficacy of the system, and what burdens and benefits may flow from regulatory changes. The following sections describe the debate and proposed legislation on these topics.

Periodic Reassessment. Given the breadth and complexity of the issues that arise in research involving human beings, some groups have called for an ongoing process for reassessing the regulations and their impact. To provide policy-makers with ongoing input and advice, in *Responsible Research*, IOM

recommended the establishment of a nonpartisan, independent body of experts to ensure that the national protection system receives objective public advice. The body would consist of balanced representation of the perspectives of participants, a range of scientific disciplines, bioethics, and IRB experts. NBAC, as well, had recommended in *Human Participants*, that the federal government, in partnership with academic institutions and professional societies facilitate discussion about emerging human research protection issues and develop a research agenda that addresses issues related to research ethics.

Additional Resources. In order to prioritize the protection of human participants in research, NBAC stressed the need for adequate resources in addition to those required by the Common Rule (i.e., adequate meeting space and sufficient staff support for recordkeeping) (45 CFR 46.103(b)(2)). In *Human Participants*, NBAC called for the appropriation of funds to carry out the functions of NBAC's proposed federal oversight office. NBAC also recommended that federal appropriations for research programs include a separate allocation for oversight activities related to the protection of human participants, that institutions be permitted to request grant funding for IRBs and other oversight activities, and that federal agencies, other sponsors, and institutions make additional funds available for a range of oversight activities. The NBAC proposal regarding grant funding addressed, in part, NIH policy regarding grantees' ability to recover costs associated with IRB approval. According to the current policy, IRB costs[134] are not recoverable as direct expenses (they are considered to be a part of overhead), unless such costs are not included in the institution's facilities and administrative rate.[135]

Regulatory Change. In *Responsible Research*, the IOM questioned the clarity and relevancy of the Common Rule. While the HHS Secretary could modify the language of the Common Rule or other Subparts of 45 CFR 46, making changes to the Common Rule itself (45 CFR Subpart A) would be a logistically complex undertaking for HHS. Not only would HHS have to amend its own regulations (a time consuming activity in and of itself), but to keep the Common Rule "common" among the signatory agencies, HHS may also need to lead a lobbying effort to convince each of the federal agencies that follows the Common Rule to adopt the amendment. For this reason, in *Responsible Research*, IOM proposed that Congress, rather than HHS, take the necessary steps to broaden and strengthen the federal oversight system and to make appropriate Common Rule modifications as needed.

Other commentators have expressed reservations about the introduction of new regulations. Some objections are based upon regulations' potential to increase the

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[134] By one estimate, IRB activities cost each U.S. academic medical center $170,000 to $5 million per year. Jeremy Sugarman, et al., "The Cost of Institutional Review Boards in Academic Medical Centers," *New England Journal of Medicine*, vol. 352, no. 17 (Apr. 2005), p. 1825.

[135] "NIH Policy on Direct Cost Charges for IRB Review," *NIH* [NOT-OD-03-042], May 22, 2003, at [http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-03-042.html], visited Apr. 11, 2005.

cost of bringing new drugs to market.[136] The average cost of developing a new prescription medicine was estimated to be $400 million - $800 million in 2001, and rapidly increasing.[137] Another set of objections have focused on the effect that regulations have on the timing of bringing a drug to market, and the resulting loss of life that may result from regulatory delays.[138] These concerns have led some to urge caution when considering the implementation of new regulations governing clinical trials.

Proposed Legislation Affecting Future Human Subjects Protections. H.R. 3594 (108th Congress) would have required each institution served by an IRB to annually submit to the Secretary a report that compiles data on the number of new research proposals reviewed, the number of continuing research projects reviewed, the number of reviewed biomedical research proposals, the number of reviewed behavioral or social sciences research proposals, and any additional information determined appropriate by the Secretary. In addition, the Secretary may have required an institution to submit such reports regarding the IRB as the Secretary determined to be appropriate. The bill would have also enabled the HHS Secretary to permit individual Federal agencies to create additional protections for human subjects research that they fund or conduct.

H.R. 3594 (108th Congress) would have authorized the appropriation of $20,000,000 for FY2004 for OHRP to carry out its compliance and enforcement responsibilities, and for its Director to carry out certain responsibilities related to protecting human subjects. Further, the bill would have allowed institutions to recover costs associated with compliance for human subject protections under this part from government sponsors of research as direct costs. In addition, the OHRP Director would have been able to make grants for the development of a model education program to be used by institutions served by IRBs, as well as to facilitate minority recruitment on IRBs. The bill would have authorized to be appropriated such sums as may have been necessary to support the model education program.

S. 3060 (107th Congress) would have addressed the topic of funding for human subjects protections and regulatory change by authorizing the appropriation of $20,000,000 to establish the National Office of Human Research Protections, and to develop standards of practice. It would have also authorized the appropriation of

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[136] See, e.g., Gillian A. Hood, "A Perspective from One Clinical Research Center in the United Kingdom," *Applied Clinical Trials*, (May 1, 2004), at [http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=94508], visited Apr. 11, 2005.

[137] See, e.g., "Tufts Center for the Study of Drug Development Pegs Cost of a New Prescription Medicine at $802 Million," *Tufts University News Release* (Nov. 30, 2001), at [http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=6], visited Apr. 11, 2005; and Kevin Davies, "Counting the Cost of Drug Discovery," *Bio IT World* (July 11, 2002), at [http://www.bio-itworld.com/archive/071102/firstbase.html].

[138] See, e.g., Dale H. Gieringer, "Compassion vs Control: FDA Investigational-Drug Regulation," *Cato Policy Analysis*, no. 72, (May 20, 1986), describing the loss of life from delayed clinical trials and limited access to AIDS drugs, at [http://www.cato.org/pubs/pas/pa072.html], visited Apr. 11, 2005.

$15,000,000 for demonstration grants to improve IRB function, and other sums as necessary to have carried out the act.

Appendix A: The Common Rule's (and 45 CFR 46's) Interaction with FDA Regulations and the HIPAA Privacy Rule

A variety of regulations can impact the conduct of human subjects research. As discussed in previous sections, these include not only the Common Rule and other parts of 45 CFR 46, but also the HIPAA Privacy Rule (45 CFR 164), and FDA regulations (21 CFR 50, 56). Conversations have arisen regarding how best to protect human subjects in light of the sometimes conflicting requirements of the various regulations. The information in this appendix summarizes the debate and proposed legislation focused on the interaction of the Privacy Rule and the FDA regulations with the Common Rule and some other portions of 45 CFR 46.

The HIPAA Privacy Rule

The Privacy Rule established a set of national standards for the protection of certain health information. HHS issued the Privacy Rule to implement the Health Insurance Portability and Accountability Act of 1996 (HIPAA, P.L. 104-191). The Privacy Rule regulates the use and disclosure of *protected health information* (PHI) (which is generally defined as individually identifiable health information) by *covered entities* (which are health plans, health care clearinghouses, and health care providers who transmit any health information in electronic form in connection with a transaction for which HHS has developed standards, e.g., Medicare claims).[139] Examples of PHI include: name, address, birth date, social security number, diagnosis, and more.[140] The Privacy Rule requires IRBs or *privacy boards*[141] to review requests for information and carry out its provisions. The Privacy Rule may thus create some new responsibilities for some IRBs.

The Privacy Rule prohibits a covered entity from disclosing PHI for research without the patient's authorization (45 CFR 164.508(a)(1)),[142] whereas the Common Rule requires informed consent in order to conduct research on a subject (45 CFR 46.116). The Privacy Rule specifically permits authorization to be combined with informed consent (45 CFR 164.508(b)(3)(i)). In addition, in some circumstances — including the conduct of research — the Privacy Rule's requirements may be

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[139] 45 CFR 160.103. See also, HHS, OCR, "Summary of the HIPAA Privacy Rule," May 2003, at [http://hhs.gov/ocr/privacysummary.rtf], visited Apr. 11, 2005.

[140] Protected health information means individually identifiable health information, except as otherwise provided in 45 CFR 160.103. *See also* HHS, Office for Civil Rights (OCR), "Privacy Brief: Summary of the HIPPA Privacy Rule," at [http://www.hhs.gov/ocr/privacysummary.pdf], visited Apr. 11, 2005.

[141] A privacy board is defined in 45 CFR 164.512(i)(1)(i)(B).

[142] The Privacy Rule specifically permits authorization to be combined with informed consent 45 CFR 164.508(b)(3)(I). In addition, in many circumstances, including the conduct of research, the Privacy Rule's requirements may be satisfied by either informed consent or authorization. See, e.g., 45 CFR 164.532(a).

satisfied by either informed consent or authorization(see, e.g., 45 CFR 164.532(a)). Authorization's requirements are tailored to its purpose of giving permission to disclose a person's personal health information.[143] Those of informed consent are tailored to its purpose of giving permission to conduct research on the person him or herself.[144]

The Privacy Rule and the Common Rule may jointly govern some research, but apply differently from one another in the following key areas:

1. ***Scope***. The Privacy Rule has a different scope than the Common Rule. While the Common Rule attaches when there is a federal funding source (45 CFR 46.101), the Privacy Rule applies regardless of funding source, but restricts only the actions of *covered entities*: health plans, health care clearinghouses, and health care providers who transmit any health information in electronic form in connection with a transaction for which HHS has developed standards (e.g., Medicare claims).[145] The Privacy Rule restricts covered entities' disclosure of PHI, whether in an electronic or other form.

2. ***Background Research***. The Privacy Rule requires no oversight in one circumstance where the Common Rule necessitates prior IRB review. The Privacy Rule permits a covered entity to use and disclose PHI for research purposes, without an individual's authorization, provided the covered entity obtains representations from the researcher that the use or disclosure of the PHI is solely to prepare a research protocol or for similar purpose preparatory to research, that the researcher will not remove any PHI from the covered entity, and that PHI for which access is sought is necessary for the research.[146] The Common Rule would classify the same background investigation into patient health records as "human subjects research" and would thus require prior IRB approval (45 CFR 46.102(d), (f)(2)).

3. ***Databases, Repositories, and Unspecified Future Research***. The Privacy Rule requires a patient's authorization for the release of PHI, in some cases in which the Common Rule does not require informed consent. To obtain PHI from a database or repository, or to reuse it in the future, the Privacy Rule requires the researcher to obtain the specific authorization of each individual whose health information was procured, specifically prohibiting the combination of

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[143] For a complete list of the requirements for authorization, see 45 CFR 46.508(c).

[144] For a complete list of the elements of informed consent, see 45 CFR 46.116.

[145] 45 CFR 160.103. See also HHS, OCR, "Summary of the HIPAA Privacy Rule," May 2003, at [http://hhs.gov/ocr/privacysummary.rtf], visited Apr. 11, 2005.

[146] 45 CFR 164.512(i). According to the same provision, a covered entity may also disclose PHI without an individual's authorization, provided the covered entity obtains either: (1) documentation of a waiver approval by an IRB or privacy board; or (2) in certain circumstances, representations from the researcher that the use or disclosure sought is solely for research on decedents' PHI. Section 164.512(j) makes allowances for disclosure without authorization to avert a serious threat to health or safety. Section 164.514(e) provides that a covered entity also may use or disclose a limited data set of PHI (largely anonymized data) for research purposes without an individual's authorization.

authorizations for various research projects (compound authorization) (45 CFR 164.508(b)(3)).[147] The Common Rule contains no equivalent prohibition. Some who conduct registry or database research have questioned the necessity of obtaining specific authorization for each disclosure as the Privacy Rule requires, claiming that the requirement is burdensome, and that other adequate privacy safeguards could be implemented.[148]

4. ***Post-Mortem Research***. The Privacy Rule has a requirement regarding research on cadavers that the Common Rule does not. The Privacy Rule's definition of "individual" is not limited to living persons.[149] Therefore the Privacy Rule would require researchers to obtain authorization from a legal representative of the deceased before conducting research on deceased persons. The Common Rule limits its definition of "human subjects" to the living, and therefore does not apply to post-mortem research (45 CFR 46.102(f)).

5. ***IRB Role***. While privacy and confidentiality issues are involved in all forms of research involving human participants, the focus of IRB review under the Common Rule is to protect the *safety* of individuals enrolled in clinical research.[150] However, in the rapidly expanding field of health services research (HSR),[151] which typically involves the secondary analysis of large databases of medical records previously collected for other purposes, the principal risk to participants is not physical harm, but a loss of privacy. The Common Rule specifies that IRBs may only approve research that is judged to have adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, (45 CFR 46.111(a)(7)), and requires that informed consent include a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained (45 CFR 46.113(a)(5)). Even so, it does not provide any additional requirements, stipulate acceptable protection provisions, or define terms. The Privacy Rule may thus significantly expand the function of IRBs, by requiring them to weigh the potential threats to privacy before granting a researcher access to participants' medical information without their authorization.[152]

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[147] There are a few exceptions to this requirement, specified in 45 CFR 164.532.

[148] See, e.g., Julie Ingelfinger and Jeffrey Drazen, "R egistry Research and Medical Privacy," *New England Journal of Medecine*., vol. 350, no. 14 (Apr. 1, 2004), p. 1452.

[149] 45 CFR 164.502(f): A covered entity must comply with the requirements of this Subpart with respect to the protected health information of a deceased individual; 45 CFR 160.103: *Individual* means the person who is the subject of PHI.

[150] The emphasis of subject's emphasis is reflected throughout the Common Rule, and prominently in its title: Federal Policy for the Protection of Human Subjects.

[151] Health services research is the study of the effects of using different modes of organization, delivery, and financing for health care services. Its focus is on the effectiveness of health care interventions in a real-world setting, whereas clinical research concentrates on the efficacy of interventions in the controlled setting of a clinical trial.

[152] The preamble to the Privacy Rule notes that waivers will rarely apply to clinical trials, because the researchers are likely to have contact with the research subjects and be able to

(continued...)

Groups representing the biomedical research community have expressed concern over the Privacy Rule's impact on research previously only governed by the Common Rule. A survey conducted by the *Association of American Medical Colleges* found that the Privacy Rule had the following effects on research:[153]

- Research subjects were confused and distracted by having to both *consent* to participate in research (as per the Common Rule) and *authorize* use of their PHI (as per the Privacy Rule).
- Collaborations became more difficult because the Privacy Rule requires *authorization* for PHI to be shared among institutions, and the Common Rule does not.
- The quality of research was diminished, and research costs were raised because of the *authorization* requirements, which require a subject to assent before each separate disclosure of their PHI. The Common Rule has been interpreted to allow a one-time consent for research.

The positive effects of the Privacy Rule on individual privacy are more difficult to document. However, it does make explicit requirements that must be met before personally identifiable health information can be disclosed.

The interaction of the Privacy Rule and the Common Rule was one topic addressed by the SACHRP. At a meeting in March 2004, SACHRP created a drafting committee to develop recommendations concerning the revision of the Privacy Rule to achieve greater harmonization with the Common Rule, ensure protection of privacy rights, and reduce the regulatory burden.[154]

Food and Drug Administration

The FDA is the HHS agency responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, and for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable. FDA also helps the public obtain the accurate, science-based information

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[152] (...continued)
seek authorization to use their medical information. Waivers are more likely to be sought in HSR. Investigators conducting HSR may not have the ability to contact the original subjects, and even if locating them is theoretically possible, the number of individuals may be far too large to make contacting them practicable.

[153] Susan H. Ehringaus, "AAMC Project to Document the Effects of HIPAA on Research," *presentation to HHS SACHRP*, Alexandria, VA, March 30, 2003, at [http://www.hhs.gov/ohrp/sachrp/mtgings/mtg03-04/hipaaaamc_files/frame.htm], visited Apr. 11, 2005.

[154] HHS, SACHRP, public meeting, Alexandria, VA, March 2004, at [http://www.hhs.gov/ohrp/sachrp/mtgings/mtg03-04/mtg03-04.htm], visited Apr. 11, 2005.

they need to use medicines and foods to improve their health.[155] In keeping with its mission, the FDA regulates clinical research on human subjects that generates data to support a company's application for marketing (21 CFR Parts 50 and 56).

FDA regulations overlap with the Common Rule and other Subparts of 45 CFR 46 in instances in which federally funded research is used to generate data for marketing applications. As early as 1981, the FDA indicated that its regulations governing human research subject protections and those governing IRB organization and function were drafted to be as consistent as possible with the Common Rule. (46 Federal Register 8942 and 46 Federal Register 8942) However, differences between FDA regulations and the Common Rule, as well as other Subparts of 45 CFR 46 do exist, as do differences in the agencies' statutory authority and functions.

Harmonization of the regulations has been a topic of much discussion, the focus of a SACHRP subcommittee established in October 2004, and the target of some proposed legislation. The following are some key differences between FDA regulations and the HHS Regulations, which might be affected by harmonization:

(1) ***Scope***. Where the Common Rule covers most basic and clinical research conducted using federal funds (including social or behavioral research),[156] FDA regulations focus only on clinical investigations which support marketing applications from companies seeking to place biomedical products in interstate commerce. (21 CFR 50.1(a)) The difference in scope of the two sets of regulations is relevant to harmonization efforts for two reasons. First, both sets of regulations may apply to some research, which may create difficulty for researchers when their requirements are dissimilar. Second, there are reports of research not covered by either set of regulations, and therefore without any of the federal human subjects protections that they provide.

(2) ***Definitions***. The Common Rule specifies that a human subject must be living (45 CFR 46.102(f)), FDA does not.[157] Only FDA has distinct definitions for investigator and sponsor(21 CFR 50.3(d), (e), and (f)). (By contrast, the Common Rule defines institution, and research subject to regulation (45 CFR 46.102(b) and (e)).)

(3) ***Emergency Use***. FDA allows investigators to use test articles (unapproved medicines or devices)[158] without the consent of human subjects in certain

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[155] FDA, "FDA's Mission Statement," at [http://www.fda.gov/opacom/morechoices/mission.html], visited Apr. 11, 2005.

[156] 45 CFR 46.101. This provision lists a detailed description of who is covered by the regulation, including some exceptions for anonymized data for educational testing.

[157] "Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient"(21 CFR 50.3(g)).

[158] "Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other (continued...)

emergency situations. Highlights of the seven conditions that must be met include the following: the human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.[159] While HHS has adopted its own emergency use provision,[160] the Common Rule as adopted by signatory federal agencies and departments has no emergency use provision.

(4) ***Financial Conflicts of Interest***. Both the Common Rule and FDA regulations state that no member of IRB may participate in IRB's initial or continuing review in which the member has a conflicting interest (45 CFR 46.107(e) (HHS); 21 CFR 56.107(e) (FDA)). However, only FDA requires certification and disclosure of financial conflicts for *investigators* (21 CFR 54).

(5) ***International Research***. Both the Common Rule and FDA regulations apply to research conducted outside of the United States, provided that it falls within their respective scopes. However, the Common Rule allows a department or agency head to approve the substitution of foreign procedures in lieu of its own if he or she determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in the Common Rule (45 CFR 46 46.101(h)). FDA regulations to not allow department or agency heads to waive FDA regulations' requirements to conduct a foreign clinical trial under an IND. However, the FDA regulations do contain provisions for incorporating the results of a foreign clinical trial not conducted under an IND into an application for marketing, provided that the study was well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community (e.g., the Declaration of Helsinki) (21 CFR 312.120).

(6) ***Parental Consent***. Both 45 CFR 46 (Subpart D — which is not a part of the Common Rule) and FDA generally require the permission of a parent or guardian and the assent of the child for a child to participate in a clinical trial (45 CFR 46.408(b) (HHS); 21 CFR 50.55(e) (FDA)). However unlike FDA, Subpart D further stipulates that the IRB may waive the parental consent requirement if it is not reasonable to protect the subjects (e.g., abused or neglected children). In that case, an alternative appropriate mechanism for protecting the children can be substituted (45 CFR 46.408(c)).

Proposed Legislation Related to Harmonization. H.R. 3594 (108th Congress) would have required harmonization of 45 CFR 46 (including the Common

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[158] (...continued)
article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n)" (21 CFR 50.3(j)).

[159] The lengthy set of FDA's rules regulating *Emergency Use* appear at 21 CFR 50.24.

[160] 45 CFR 46.101(i) allows a waiver of the informed consent requirements of 45 CFR 46 in certain narrowly defined types of research in emergency situations (61 Federal Register 51531[Oct. 2, 1996]).

Rule) and FDA regulations within three years, followed by formal rule-making. In preparation, the bill would have required that the HHS Secretary review the Common Rule and 21 CFR 50 and 56 not later than 18 months after the enactment of the Act. The review would have determined to what extent the differences in approach between the two sets of regulations could have been harmonized, with the goal of having only such differences remain as reflected the legal or factual variations in the human subject research. The areas of difference reviewed would have included (but would not have been limited to) differences regarding the existence of a significant financial interest; provisions for research relating to emergency interventions; the definition of *institution*; and requirements for attestations by clinical investigators regarding the protection of human subjects.

H.R. 3594 (108th Congress) would have also required the Secretary to publish in the Federal Register, not later than 18 months after the enactment of the Act, a determination regarding whether research with data that do not involve any interaction or intervention with a living human should be considered human subject research. S. 3060 (107th Congress) did not address harmonization between agencies per se, but would have applied all of the 45 CFR 46 Subparts to as broad a range of research as possible, regardless of where it was conducted, by what agency it was funded, or whether it was conducted for an application for FDA.

Appendix B. History and Requirements of the Common Rule.

International Codes and Declarations

The first sets of rules governing biomedical research arose from international traditions and agreements. The emergence of three notable sets, the Hippocratic Oath, the Nuremberg Code, and the Declaration of Helsinki, document the shift from a paternalistic research model, assuming that the physician knew best, to an autonomous model, mandating full understanding by and consent of subjects. Not until 1962 did the United States created its own set of regulations.

Hippocratic Oath: Doctor Knows Best. Prior to the 1940s, biomedical research was subsumed by the practice of medicine. Research was conducted primarily by physicians in clinical settings, with little or no external review, oversight, or informed consent. No research-specific ethical or legal framework controlled investigations was in place.

Medical practice and research were governed by the Hippocratic Oath, the first set of Western writings about medical practice. The Oath was rooted in the ethical principles of non-maleficence (directing physicians not to harm patients) and beneficence (directing physicians to benefit patients), with little concern for autonomy (directing physicians to respect the informed decisions of patients). One version of the Oath advised the wisdom of "concealing most things from the patient while you are attending to him, . . . turning his attention away from what is being done to him, . . . [and] revealing nothing of the patient's future or present condition."[161]

The Hippocratic Oath placed decisions about medical care and research in the hands of physicians who had more scientific and medical knowledge than their patients. Decision-making by lay-person was perceived to be a burden physicians should alleviate rather than a right they should respect.

Nuremberg Code: Subject's Choice. In the 1940s, the wake of the Holocaust changed the research paradigm, when Nazi doctors with recognized medical credentials performed "medical experiments without the subjects' consent, upon civilians. . . [resulting in] murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts."[162] As a part of the judgement against the physicians, the first ethical research principles were enacted in the Nuremberg Code. The Code was not specifically adopted into United States law, but later became a basis for a Department of Defense policy and the regulations that govern the protection of human subjects in most federally funded research in the United States: 45 CFR 46.

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[161] Ruth Faden and Tom Beauchamp, *A History of Informed Consent* (Oxford: Oxford University Press, 1986), p. 2.

[162] *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law no. 10. Nuremberg, October 1946-April 1949*, (Washington: GPO, 1949-1953), p. 11.

Topping the list of principles listed in the Nuremberg Code was a requirement that a researcher obtain voluntary consent of the human subject.[163] Medical researchers were to no longer make decisions on their subjects' behalf, but instead were to effectively convey information about the proposed research to competent potential subjects, and allow them to decide whether to participate. This was a dramatic shift in practice.

Subsequent provisions in the Nuremberg Code instructed researchers to ensure that the potential benefits outweighed the risks of research, and to minimize those risks. Researchers were also prohibited from causing permanent harm or death to their subjects.

The Nuremberg Code did not resolve all possible issues. It lacked detail, failing both to describe how consent was to be obtained, and was not capable of handling complex issues arising out of advances in social science and biomedical research.[164] The Code was also not immediately accepted by some researchers in the United States, who conducted subsequent studies on populations lacking the capacity to consent, such as the mentally retarded (lacking the element of comprehension) and prisoners (lacking the element of free will).[165]

Declaration of Helsinki: Physicians Sign On. In 1964, the World Medical Association created its own code to help maintain public trust in biomedical research: the Declaration of Helsinki.[166] It was the first code prescribed by an internationally recognized body of medical professionals that embraced the concept of informed consent. However, it allowed physicians considerable latitude when conducting research with the hope of saving life, re-establishing health, or alleviating suffering.[167] Physicians conducting this therapeutic research were instructed to obtain informed consent "consistent with patient psychology,"[168] implying that consent was not needed if it were inconsistent with patient psychology, a term the Declaration did not define. This therapeutic loophole was closed in later amended versions of the Declaration.[169]

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[163] *Trials of War Criminals Before the Nuremberg Military Tribunals*, pp. 181-182.

[164] Faden and Beauchamp, *A History and Theory of Informed Consent* p. 156.

[165] David J. Rothman, *Strangers at the Bedside* (New York: Basic Books, 1991), p. 62.

[166] Faden and Beauchamp, *A History and Theory of Informed Consent,* p. 156.

[167] "Human Experimentation: Code of Ethics of the World Medical Association," *British Medical Journal*, vol. 2, no. 177 (1964).

[168] Ibid. A situation in which consent might be inconsistent with patient psychology might be, for example, one in which informed consent would require the disclosure of a previously-unrevealed illness that a treating physician wished to conceal, so as not to impede the healing process by distressing the patient.

[169] *World Medical Association Declaration of Helsinki*, Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, Oct. 1975, 35th WMA General Assembly, Venice, Italy, Oct. 1983, 41st WMA General Assembly, Hong Kong, Sept. 1989, 48th WMA General (continued...)

United States Regulations Before the Common Rule

Congress has been involved in the examination of biomedical ethics issues since the1960s, and played a vigorous role in the early history of federal involvement in protecting human research subjects. Much of this was spurred by public disclosures of events that involved morally unacceptable and often dangerous investigations on human subjects. The HHS (formerly DHEW), was the first federally funded agency to openly develop formal policies for the protection of human subjects.[170] Most of the details of the initial policies in this area were developed by two HHS agencies, the NIH, and the FDA.[171]

NIH Clinical Center Policy of 1953. In 1953, the NIH opened its Clinical Center to conduct biomedical research. That same year, in the shadow of the Nazi medical experiments, the NIH Director adopted an intramural policy requiring informed consent and "group consideration" of clinical research procedures that "deviated from acceptable medical practice or involved unusual hazard."[172] The policy introduced the notion that some, though not all research protocols should be reviewed by someone other than the principal investigator in the study. However, it only applied to some NIH research protocols, and it had no application to research conducted outside of NIH. Officials anticipated widespread adoption and use of this policy by other federal agencies, though it never occurred.[173]

Drug Amendments of 1962. Two years prior to the enactment of the Declaration of Helsinki, the births of deformed infants whose mothers had taken a sedative called thalidomide, focused public attention on pending United States

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[169] (...continued)
Assembly, Somerset West, Republic of South Africa, Oct. 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, Oct. 2000.

[170] In 1953, Secretary of Defense Charles Wilson issued a top secret memorandum establishing policy for research related to atomic, biological, and chemical warfare. The policy incorporated the principles of the Nuremberg Code and two additional protections — a prohibition on research involving prisoners of war and a requirement that the Secretary of the appropriate military service approve research studies. National Bioethics Advisory Commission, Ethical and Policy Issues in Research Involving Human Participants, Aug. 2001, p.151.

[171] FDA did not become part of HHS until 1968.

[172] NIH, *Group Consideration of Clinical Research Procedures Deviating from Accepted Medical Practice of Involving Unusual Hazard*, (Memorandum, approved by the Director, NIH, 1953), cited in, John C. Fletcher, "Location of the Office for Protection from Research Risks Within the National Institutes of Health: Problems of Status and Independent Authority," in NBAC, *Ethical and Policy Issues in Research Involving Human Participants, Volume II, Commissioned Papers and Staff Analysis* (Bethesda: NBAC), p.B-10.

[173] Faden and Beauchamp, *A History and Theory of Informed Consent*, pp. 201-202.

legislation.[174] Thalidomide was widely used in Europe. Although not approved by the FDA,[175] the drug maker had supplied thalidomide to thousands of physicians in the United States to conduct clinical investigations to establish the drug's safety. Many of the women who received thalidomide in this way were not informed that they were participating in a study.[176] The drug caused some babies to be born with a rare defect known as Phocomelia Syndrome, which is characterized by missing or deformed arms and/or legs. Other symptoms may include growth and mental deficiencies, and defects in the eyes, ears, and nose.[177]

Impelled in part by the phocomelia-thalidomide connection, Congress unanimously enacted the United States' first law governing research on human beings: the Drug Amendments of 1962 (P.L. 87-781),[178] which amended the Federal Food, Drug, and Cosmetic Act of 1938. The Amendments instructed the then DHEW Secretary to issue regulations requiring FDA to review new drugs for efficacy as well as safety, and to obtain subjects' informed consent for research. A proposal from Senator Jacob Javits would have required informed consent prior to the administration of any investigational drug, however other Senators voiced concerns that such a requirement would adversely affect physician-patient relationships.[179] As a result, FDA's regulations allowed researchers to forego the consent process if they deemed it not feasible or in their professional judgement, contrary to the best interests of such human beings (Food, Drug, and Cosmetic Act, § 505, 520).

Following the publication of FDA regulations, concerns emerged that their consent provisions were poorly developed and led to ambiguities. In response, FDA published, *Consent for Use of Investigational New Drugs on Humans: Statement of Policy* in August 1966.[180] The new provisions were closely modeled after the Nuremberg Code and the Declaration of Helsinki. The regulations applied only to experimental drugs, devices, and biologics. They required researchers to advise subjects of any existing alternative therapies, to tell subjects that they could be used as study controls, and to obtain subjects' written informed consent.

Events Leading Up to the Common Rule

By mid-1960, NIH officials began to have some concerns about its regulation of human subjects research. They questioned the agency's tradition of relying exclusively on the moral character of investigators to safeguard human subjects, and

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[174] Food and Drug Administration, "The Story of the Laws Behind the Labels, Part 3, 1962 Drug Amendments,"*FDA Consumer*, June 1981, at [http://vm.cfsan.fda.gov/~lrd/histor1b.html], visited Apr. 11, 2005.

[175] At the time, FDA's prior approval of investigational studies was not required.

[176] Congressional Record, Aug. 23, 1962, pp. 17395-17403.

[177] For further information about Phocomelia Syndrome, see [http://my.webmd.com/hw/health_guide_atoz/nord780.asp], visited Apr. 11, 2005.

[178] Section 505(i) of the Food, Drug, and Cosmetic Act of 1962.

[179] Rothman, *Strangers at the Bedside*, pp. 63-67.

[180] Faden and Beauchamp, *A History and Theory of Informed Consent*, p. 204.

its lack of systems to monitor the conduct of its investigators. Since the end of World War II, NIH's budget had grown from $2.8 million in 1945 to $773.1 million in 1965 (a 276-fold increase).[181] In 1965, NIH awarded 11,000 research grants, about one-third of which involved human experimentation.[182]

Reports of Unethical Practices. In January 1962, the Law-Medicine Research Institute in Boston (MA) published results of a DHEW-funded survey of research practices in medical departments. Of the respondents,[183] only a few had procedural guidelines governing human subjects research, and about a third had special consent forms for research projects. In addition, most institution officials considered even self-regulation by committees unacceptable, preferring to leave these procedures exclusively to investigators. The report concluded that internal institutional regulation of research was erratic.[184]

In November 1964, NIH Director Shannon received a report from the agency's research resource division. It warned of "possible repercussions of untoward events which are increasingly likely to occur" in "unfavorable" circumstances, including events that could "rudely shake" the NIH. The report cited the absence of an applicable code of conduct for research and an uncertain legal context as specific concerns, among others.

In 1966, Henry Beecher published 22 detailed cases of research which contained serious or potentially serious ethical violations. Only two studies mentioned obtaining informed consent. Others allowed subjects to suffer preventable illness and even death, replacing known therapies with placebos. In one study, control subjects with typhoid fever did not receive chloramphenicol (a recognized treatment), resulting in the preventable deaths of an estimated 23 patients.[185]

1966 Surgeon General's Policy. On February 8, 1966, the United States Surgeon General responded to the criticism by publishing a new policy: "Clinical Investigations Using Human Subjects." The policy required all PHS-funded institutions to provide prior review by a committee for proposed investigations with human subjects. The committees were charged with assessing the rights and welfare of the research subject, the appropriateness of informed consent method, and the balance of risks and benefits. (21 CFR 310.102(f)) The policy, while addressing the issue of self-regulation, did not adequately define key terms such as "rights and

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[181] NIH, Office of the Director, *NIH Almanac 2002*,NIH Publication No. 02-5, December 2002, at [http://www.nih.gov/about/almanac/appropriations/part2.htm], visited Apr. 11, 2005.

[182] Rothman, *Strangers at the Bedside*, p. 54.

[183] Eighty-six (86) surveys were sent out, and fifty-two (52) institutions responded.

[184] "A Study of the Legal, Ethical, and Administrative Aspects of Clinical Research Involving Human Subjects: Final Report of Administrative Practices in Clinical Research," [NIH] Research Grant No. 7039 Law-Medicine Research Institute, Boston University, 1963 (ACHRE No. BU-053194-A).

[185] Henry K. Beecher, "Ethics and Clinical Research," *New England Journal of Medicine*, vol. 274, no. 24 (Jun 16, 1966), pp. 1354-1360.

welfare of potential subjects," "informed consent," and risks and potential benefits." According to one account, the lack of definitions confused committees and led to arbitrary application of the policy.[186]

1971 DHEW Guide. In 1971, DHEW expanded the Surgeon General's policy and defined many of the missing terms in its "Institutional Guide to DHEW Policy on Protection of Human Subjects." The Guide offered clarifications, such as a listing of the elements of informed consent, and added a requirement that ongoing research projects be continually reviewed.[187] However, issues remained regarding the composition of the institutional review committees, compensation for injury during an investigation, ensuring an equitable research subject selection process, and the achievement of adequate informed consent.[188]

The Tuskegee Study. In July 1972, Jean Heller, a reporter with the Associated Press, released a story about a PHS-funded study that shocked the public and the research community: the Tuskeegee syphilis study. As documented in the book *Bad Blood*,[189] to investigate the continuing effects of syphilis, PHS-funded researchers withheld treatment from hundreds of African-American men in Tuskeegee, Alabama for 40 years (19 years past the discovery of penicillin, which can cure the disease). The untreated disease left many men blinded, insane, and even dead.

A DHEW ad hoc advisory committee investigation of Tuskeegee found that the study was ethically unjustified, and that penicillin therapy should have been made available to all study subjects when it was made available for treatment of syphilis.[190] The panel also found that neither DHEW, nor any other government agency had policy in place to adequately review experimental procedures, or to adequately obtain informed consent from research subjects. It recommended that Congress create a permanent body with authority, at a minimum, to regulate all federally supported and conducted research involving human subjects.

DHEW and Congress Take Action. On May 30, 1974, DHEW replaced its 1966 policy by publishing more robust and comprehensive regulations governing the protection of human subjects. (45 CFR 46) One month later, Congress passed the *National Research Act* (Pub. L. 93-348), which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission) and directed it to make recommendations to the DHEW Secretary about the ethical principles that should underlie human subjects research.

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[186] Faden and Beauchamp, *A History and Theory of Informed Consent*, p. 211

[187] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Protecting Human Subjects*, GPO 040-000-00452-1, Dec. 1981, p. 22-23.

[188] Faden and Beauchamp, *A History and Theory of Informed Consent*, p. 213.

[189] James H. Jones, *Bad Blood* (New York, Free Press, 1981 and 1993).

[190] J. S. Reiser, et al., *Ethics in Medicine, from Final Report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel*, [reprinted from the Final Report; Washington, D.C., United States PHS, pp. 5-15] (Cambridge, MA: MIT Press, 1977).

The Act also required grantees and contractees under the Public Health Service Act to establish IRBs to review research involving human subjects.

45 CFR 46, Subpart A: The Basis of the Common Rule

Subpart A of the 1974 regulations — basic HHS Policy for Protection of Human Research Subjects — was adopted by a many, but not all, federal agencies on June 18, 1991. It became known as the *Common Rule* (56 Federal Register 28003)

The final form of the Common Rule and its adoption by agencies other than HHS were due in large part to the recommendations of two Commissions. The first, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (The National Commission), was created on July 12, 1974 with the passage of the National Research Act (P.L. 93-348). The Act also required grantees and contractees under the Public Health Service Act to establish IRBs to review research involving human subjects. The National Commission was directed to consider, among other things, the ethical principles that should underlie human subjects research. Its work culminated in the issuance of the Belmont Report,[191] which sets forth the following three principles:

- *Principal of Respect for Persons:* Consideration must be given to individuals' autonomy. (This principle underlies the requirement of obtaining informed consent.)
- *Principal of Beneficence:* Research must be shown to be beneficial and reflect the Hippocratic ideal of doing no harm.
- *Principle of Justice:* The potential benefits of research must be balanced against the risks to subjects.

In 1980, DHEW official became HHS, and in response to the Belmont Report, the HHS and the FDA significantly revised their human subjects regulations in 1981 (45 CFR 46; 21 CFR 50).

The second commission responsible for the adoption of the Common Rule was the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (the President's Commission). From 1982-1983, the President's Commission analyzed the adequacy and uniformity of the rules and procedures of some 23 Federal entities reporting that they conducted or supported research with human subjects. In its final report, "Implementing Human Research Regulations: The Adequacy and Uniformity of Federal Rules and of Their Implementation," it found that the DHEW 1974 policy was the benchmark of "adequacy" for protecting human research subjects.[192]

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[191] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Belmont Report*, Apr. 18, 1979, (OS) 78-0013 and No. (OS) 78-0014, (Washington: GPO).

[192] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *The Adequacy and Uniformity of Federal Rules and of their* (continued...)

Basic Requirements of the Common Rule. The Common Rule was broader, and more comprehensive than the 1971 DHEW guide. It contained the following basic requirements (for a comprehensive list, see 45 CFR 46, Subpart A):

- *Intramural and Extramural Application.* The Common Rule applied not only to research conducted outside of NIH as the 1966 regulations had, but also that conducted on NIH's campus.
- *Institutional Assurances.* Each institution that conducts research involving human subjects must first submit written "assurance" satisfactory to the department or agency head that it will comply with the requirements in 45 CFR 46, including a statement of human subjects protection principles (e.g., Nuremberg Code, Helsinki Code). The institution also must certify that the research has been reviewed and approved, and will be subject to continuing review by an IRB provided for in the assurance.
- *Broader, Ongoing IRB Review.*
- *Review of all protocols.* The new policy required external review of all human subjects research, not just those judged by the principal investigator to present risk to human subjects.[193] The IRBs, and not investigators, would determine the extent of any risk involved and check the informed consent protocols.
- *Conduct Ongoing Review*. IRBs would be required to periodically re-review ongoing research.
- *Meet Membership Requirements.* The IRB must be composed of a minimum of five qualified members of varied backgrounds.
- *Specified Informed Consent Requirements.* The basic elements of informed consent are as follows (additional elements of informed consent for specific circumstances can be found in 45 CFR 46.116.):
- A statement that the study involves research, an explanation of the purposes of the research as well as the expected duration of the subject's participation, a description of the procedures that will be followed, and identification of any experimental procedures;
- A description of any reasonable foreseeable risks or discomforts to the research subject;
- A description of any benefits to the research subjects or to others which may reasonably be expected from the research;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the research subject;
- A statement describing the extent, if any, to which confidentiality of records identifying the research subject will be maintained;
- For research involving more than minimal risk, an explanation about whether any medical treatments are available if injury occurs and, if

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[192] (...continued)
Implementation: Protecting Human Subjects (Washington, D.C.: GPO, 1983).

[193] Certain low-risk types of research are exempt from the requirement of IRB review, for example, research involving the use of educational tests (cognitive, diagnostic, aptitude achievement) if information from such tests is recorded in such a way that subjects cannot be identified. For other exemptions, see 45 CFR 46.101.

so, what they consist of, or whether further information may be obtained;

- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the research subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.