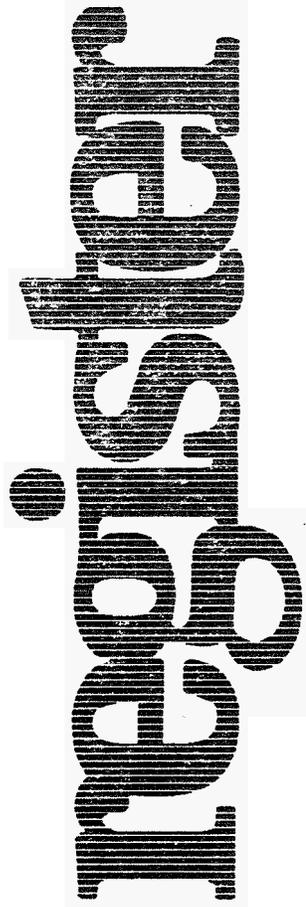

Monday
January 26, 1981



Part X

**Department of
Health and Human
Services**

Office of the Secretary

Public Health Service Human Research
Subjects

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Office of the Secretary
45 CFR Part 46
Final Regulations Amending Basic HHS Policy for the Protection of Human Research Subjects

AGENCY: Department of Health and Human Services.

ACTION: Final rule.

SUMMARY: The Department of Health and Human Services (HHS or Department) is amending the HHS policy for the protection of human research subjects and responding to the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (President's Commission) concerning institutional review boards (IRBs).

These amendments substantially reduce the scope of the existing HHS regulatory coverage by exempting broad categories of research which normally present little or no risk of harm to subjects. Specifically, the new regulations: (1) Exempt from coverage most social, economic and educational research in which the only involvement of human subjects will be in one or more of the following categories: (a) The use of survey and interview procedures; (b) the observation of public behavior; or (c) the study of data, documents, records and specimens. (2) Require IRB review and approval of research involving human subjects if it is supported by Department funds and does not qualify for exemption from coverage by these regulations. (3) Require only expedited review for certain categories of proposed research involving no more than minimal risk and for minor changes in research already approved by an IRB. (4) Provide specific procedures for full IRB review and for expedited IRB review. (5) Designate basic elements of informed consent which are necessary as a prerequisite for humans to participate as subjects in research, and additional elements of informed consent which may be added when they are appropriate. (6) Indicate circumstances under which an IRB may approve withholding or altering some or all of the elements of informed consent otherwise required to be presented to research subjects. (7) Establish IRB membership requirements. (8) Establish regulations

which, to the extent possible, are congruent with FDA final regulations to be published on informed consent and IRB activities.

The notice of proposed rulemaking (NPRM) which preceded this final regulation was controversial in two respects: (1) It proposed prior IRB review and approval of human subject research activities not directly funded by the Department, but carried out in institutions which receive HHS funding for certain research activities; and (2) it left open the question of coverage of behavioral and social science research involving little or no risk to the human subjects. The Department expects these controversies to be resolved because the NPRM is replaced with final regulations which do not extend the requirements as described in item (1) and provide broad exemptions for behavioral and social science research described in item (2).

EFFECTIVE DATE: These regulations shall become effective on July 27, 1981, institutions currently conducting or supporting research in accord with General Assurances negotiated with HHS (formerly HEW) may continue to do so in accord with the conditions of their General Assurance. However, these institutions are permitted and encouraged to apply §§ 46.101, 46.102, 46.107, 46.108, 46.109, 46.110, 46.111, 46.112, 46.113, 46.114, 46.115, 46.116, 46.117, 46.118, 46.119, 46.120 and 46.121 as soon as it is feasible to do so. They need not wait for the effective date or the negotiation of a new assurance to begin to function in accord with the sections cited above. The Department will begin to renegotiate General Assurances on the effective date of these regulations.

Institutions conducting or supporting research in accord with a Special Assurance negotiated with the Department, shall continue to do so until such time as the assurance terminates. New Special Assurances will be negotiated in accord with the new regulations whenever feasible.

ADDRESS: Please send comments or requests for additional information to: F. William Dommel, Jr., J.D., Assistant Director, Office for Protection from Research Risks, National Institutes of Health, 5333 Westbard Avenue, Room 3A-18, Bethesda, Maryland 20205. Telephone: (301) 496-7163.

SUPPLEMENTARY INFORMATION: Basic regulations governing the protection of human subjects involved in research, funded by HHS (formerly HEW) were published in the **Federal Register** on May 30, 1974 (30 FR 18914).

Subsequently, regulations were published to provide additional

protections for "special groups" containing individuals who may have diminished capacity to consent or who may be at high risk. The additional regulations pertain to research activities involving fetuses, pregnant women and prisoners. They are found in Subparts B and C of 45 CFR Part 46, and they remain unchanged by the publication of these regulations except for the conforming amendments listed below.

In addition, regulations have been proposed to provide additional safeguards for other who may have diminished capacity. These were published in the **Federal Register** as follows: Research Involving Children (43 FR 31786, July 21, 1978), and Research Involving Those Institutionalized as Mentally Disabled (43 FR 53950, Nov. 17, 1978). Final regulations on these two categories are still being considered by the Department.

On August 8, 1978, the Food and Drug Administration (FDA) published proposed Standards for Institutional Review Boards for Clinical Investigations (43 FR 35186). Shortly thereafter, the National Commission submitted its report and recommendations on IRBs and informed consent, and that document was published in the **Federal Register** on November 30, 1978 (43 FR 56174). In its report, the National Commission recommended revisions of the current HHS regulations for IRBs. Because the FDA stated in the August 8, 1979 proposal that its regulations should be compatible with those of the Department, FDA withdrew that proposal and published a new proposal on August 14, 1978 in conjunction with a similar proposal published on the same date by HHS. The Department and FDA stated at that time that they agreed in principle with the recommendation of the National Commission that IRBs should operate under one set of regulations for the protection of human research subjects.

The regulations published below are nearly identical in format and content with those published by FDA in all matters pertaining to membership, functions and responsibilities of IRBs. In all other matters they are consistent with FDA regulations which differ from HHS regulations only with respect to matters covered by statute or required by the mission of FDA. The regulations published below provide a common, flexible framework within which IRBs can operate whether they are reviewing research funded by HHS or regulated by FDA.

Background

The National Research Act (Pub. L. 93-348) was signed into law on July 12, 1974, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the topics of study identified in the mandate to the National Commission was "Institutional Review Boards." The Commission was required to recommend to the Secretary, HHS, " * * * mechanisms for evaluating and monitoring the performance of Institutional Review Boards in accordance with Section 474 of the Public Health Service Act and appropriate enforcement mechanisms for carrying out their decisions." The National Commission was further required to make recommendations regarding the protection of subjects involved in research not subject to regulation by HHS.

In discharging its duties under this mandate, the National Commission studied the performance of IRBs which are required to review research involving human subjects that is conducted at institutions receiving funds for this research from HHS under the Public Health Service Act. The National Commission found that the review of proposed research by IRBs is the primary mechanism for assuring that the rights of human subjects are protected.

The National Commission undertook a substantial effort to develop information about the performance of IRBs, the research they review, and the strengths and weaknesses of this mechanism. This effort included the support of an extensive survey of IRB members, investigators and research subjects at a sample of 61 institutions including medical schools, hospitals, universities, prisons, institutions for mentally ill and retarded, and research organizations. Also, the background, development, and administration of the present HHS regulations governing IRBs were examined. Three public hearings were held at which federal officials, representatives of IRBs, investigators, and other concerned persons presented their views on IRBs. The National Minority Conference on Human Experimentation, convoked by the National Commission to assure that viewpoints of minorities would be heard, made recommendations to the National Commission that pertained to IRBs. The National Commission also reviewed several papers prepared under contract on such topics as informed consent, evaluation of risks and benefits, issues that arise in particular

kinds of research (such as social experimentation or deception research), and the legal aspects of IRB operation. A substantial amount of correspondence on IRBs was received and reviewed by the National Commission.

In addition, a survey was made of the standards and procedures for the protection of human subjects in research conducted or sponsored by federal departments and agencies. Finally, the National Commission conducted public deliberations to develop its recommendations on IRBs.

Pursuant to section 205 of the National Research Act (Pub. L. 93-348), the recommendations of the National Commission regarding Institutional Review Boards were published in the **Federal Register** (43 FR 56174) on November 30, 1978. Comments were received from approximately 100 individuals, institutions, organizations and groups. After reviewing the recommendations and the comments, the Secretary prepared the notice of proposed rulemaking which was published on August 14, 1979 (44 FR 47688).

Following the publication of the proposed rules, the Department joined FDA in holding joint hearings on them in Washington, D.C., Houston and San Francisco. Transcripts made of these meetings were considered in the preparation of the regulations. The Department received and reviewed approximately 400 sets of comments on its proposed rules. The FDA received and reviewed more than 200 sets of comments on its proposed rules. The Department and FDA then shared all of the information in both sets of comments.

On July 12, 1980 the President's Commission held hearings concerning federal regulation of behavioral and social science research. These hearings also dealt with the question of the applicability of the regulations to human subject research not directly funded by the Department. In a letter dated September 18, 1980, Chairman Abram communicated the views of the President's Commission to the Secretary, HHS.

Department officials participated in workshops, seminars and meetings sponsored by a variety of agencies, institutions and associations concerning the proposed rules. These were held in Chicago, Boston, Cleveland, New Orleans, San Antonio, Traverse City, Louisville, St. Louis and Washington, D.C. Advice was sought from a wide variety of scholars, IRB chairpersons and members, and research

investigators.

Since April of 1980 Department officials and representatives from other federal agencies have met once per week to consider all of the material relevant to the protection of human subjects compiled since the beginning of the public process in 1974. The regulations published below were prepared by them, and reviewed and approved by the Secretary.

Conforming Amendments

Subparts E and C of 45 CFR 46 are amended to correct references to specific sections of Subpart A. These changes do not represent any substantive changes to Subparts B or C, but are necessary to conform with section changes in Subpart A.

OMB Clearance

With regard to reporting and recordkeeping requirements contained in these regulations, the Department will seek Office of Management and Budget (OMB) clearance prior to use. If the OMB does not approve the reporting and recordkeeping requirements without change, the regulations will be revised to comply with OMB recommendations.

Major Provisions

The regulations continue the Department's policy of providing protections for the rights and welfare of human subjects involved in research, however, they are applicable only to research involving human subjects which is funded in whole or in part by the Department. They do not extend coverage to other research carried out by federal agencies or by non-federal institutions. By limiting applicability to research funded by HHS, the Department has made a substantial reduction in coverage from that which was proposed in the Notice of Proposed Rulemaking published in the **Federal Register** on August 14, 1979.

The regulations contain broad exemptions for educational, behavioral and social science research which involves little or no risk to research subjects. These exemptions constitute a major deregulation from rules in force at the present time. They exclude most social science research projects from the jurisdiction of the regulations.

The regulations substantially modify the existing HHS policy or protection of human subjects by reducing significantly the coverage of the policy. This is accomplished through broad exemptions of categories of research which normally present little or no risk of harm to subjects. In taking this step,

the Department anticipates that the work load of IRBs will be significantly reduced, as will the paperwork burden on those scientists whose research will henceforth be exempt. Also, since the IRB will be relieved of unnecessary work, research institutions are expected to have less difficulty in recruiting members of IRBs, and the IRBs will be able to concentrate more productively on projects which most deserve IRB attention.

These regulations, promulgated by HHS, are congruent with regulations to be published simultaneously by the Food and Drug Administration (FDA). The HHS and FDA regulations are nearly identical in both content and format in all matters pertaining to the membership, functions and responsibilities of IRBs. The two sets of regulations differ only where required to do so by statute, or where differences are dictated by the specific regulatory mission of the FDA. The congruence of the two sets of regulations is expected to remove a major source of discontent among affected institutions.

Response to Public Comment

More than 500 public comments were received by individuals and organizations in response to the publication in the **Federal Register** of (1) the Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research Institutional Review Boards (43 FR 56174 November 30, 1978), and (2) the Notice of Proposed Regulations Amending Basic HEW (now HHS) Policy for Protection of Human Research Subjects (44 FR 47688 August 14, 1979). Since the final format of the regulations varies significantly from that of the proposed regulations, the summaries of the recommendations of the National Commission report, proposed HHS regulations, public comment, and the Department's responses are organized below by topic rather than by the section and paragraph designation of the regulations. (A summary of pertinent language from the National Research Act is also included in the discussion of exemptions.) Sections and paragraphs referred to are always those of the final regulations. References to research are meant to include only research involving humans as subjects. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research is referred to as the National Commission. The major issues addressed by the commentators are considered below,

Should the Regulations Apply to HHS-Funded Research Only, or Should They be Extended to Other Research Conducted at or Supported by Institutions Receiving HHS Research Funds?

National Research Act

The Act specifies that the Secretary shall by regulation require that each entity which applies for a grant or contract under the Act for any project or program which involves the conduct of biomedical or behavioral research involving human subjects submit in or with its application for such grant or contract assurances satisfactory to the Secretary that it has established (in accordance with regulations which the Secretary shall prescribe) a board (to be known as an Institutional Review Board) to review biomedical and behavioral research involving human subjects conducted at or sponsored by such entity in order to protect the rights of the human subjects of such research (Pub. L. 93-348 Sec. 212).

Recommendation of the National Commission

The Secretary, HHS, should require by regulation that an IRB have authority to review and approve, require modification in, or disapprove all research involving human subjects conducted at the institution (43 FR 56178).

HHS Proposed Regulations: Except for categories of research specifically exempt, prior and continuing review and approval by an IRB would have been required for the conduct of all research involving human subjects not funded by HHS and conducted at or supported by any institution receiving funds from HHS for the conduct of research involving human subjects (44 FR 47698).

Public Comment: Among the more than 500 commentators, not quite 100 wrote on this issue directly, and of those commenting, a majority felt that it would be inappropriate for HHS to extend federal requirements for prior IRB review and approval to research conducted without federal funds. Objections were voiced that the regulations should be aimed at, and indeed seemed to be primarily formulated for, biomedical research. These commentators argued that if the regulations were binding on social science research (see full discussion of social science research in exemptions below), the extension of the regulations to social science research not funded by HHS was all the more onerous. A number felt that if non-HHS-funded research were to be covered by the regulations, such coverage should only

extend to categories of research in which there had been abuses of human subjects in the past. It was argued by some that HHS had no authority to extend its regulations to non-HHS-funded research, much less a clear mandate to do so. This extension, some commentators argued, would be an unwarranted intrusion on academic freedom and some felt it would violate the First Amendment to the United States Constitution by requiring prior review, thus constituting prior restraint. Among those who expressed opposition to the extension were a number of commentators who suggested that HHS encourage each institution receiving Department funds to develop its own mechanism for protecting human subjects of research not supported by HHS funds, but not require that this mechanism be the same as that required by the regulation. Several federal agencies noted that an extension of the regulations to non-HHS-funded research might conflict with their agencies' missions, if these missions were being carried out with the assistance of institutions which are receiving HHS research funds.

The Commentators: Expressing support for the extension of the HHS regulations to research not funded by the Department were in the minority. These commentators argued that IRB review procedures and criteria for approval should be consistent for all research, regardless of source of funding. Some felt, as did the National Commission, that the proposed regulations should extend compliance requirements to all research conducted at or sponsored by institutions receiving any federal funds for health research. Further, it was argued that HHS should not just require IRB review and approval of nonfederally-funded research, but that all of the provisions of the regulations should be applicable.

HHS Response: Prior to the passage of the National Research Act, HHS required by regulation (45 CFR 46) appropriate IRB review of HHS-funded research only, although many institutions conducted IRB review without regard to source of funding. Informally, HHS interpreted the Act as requiring that all research involving human subjects be reviewed by an IRB if the research was to be conducted at or sponsored by an institution applying for funding from the Public Health Service (PHS) for research of this kind. However, while awaiting the recommendations regarding IRBs by the National Commission, the requirement was implemented only at institutions where a significant portion of the human

subjects' research was supported by the Department. Institutions which conducted only a small amount of HHS-funded research were not required to conduct IRB review of non-HHS-funded research, although they were encouraged to do so. Under the proposed HHS regulations, all nonexempt research involving human subjects, regardless of the source of funding for the research, would have to have been reviewed and approved by an IRB if the research were to be conducted at or supported by an institution receiving HHS funding for this kind of research.

HHS has carefully considered its proposed policy regarding the regulation of non HHS-funded research in light of the comments received and the statutory basis for the more expansive interpretation. The public comment, including that of the President's Commission, revealed a broad based and significant amount of objection to the extension. Further, the HHS General Counsel has advised that there is no clear statutory mandate in the National Research Act to support a requirement for IRB review of other than Public Health Service-funded research. Therefore, the Secretary of HHS, after considering a number of possible options, has decided not to extend the requirements for prior IRB review and approval to non HHS-funded research.

However, since the function of these regulations is the protection of the rights and welfare of human subjects, it is of crucial importance that institutions seeking HHS funds for research demonstrate their willingness to afford human research subject protections regardless of the source of funding. The Department feels strongly that public funds for research involving human subjects, should not be awarded to institutions which are unwilling to demonstrate their dedication to this principle. The IRB mechanism is a method which has proven to be successful in achieving the protections which HHS recognizes as essential, and the Department urges institutions to continue to employ this and other appropriate methods of insuring that human research subject protections are provided for those participating in research not funded by HHS.

HHS Decision: The regulations are to be applicable only to research conducted or funded by HHS (see § 46.101(a)). However, recipients of funds for research covered by the regulations must provide "A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of

human subjects of research conducted at or sponsored by the institution, regardless of source of funding." IRB review, or some other effective mechanism for protection of human subjects, is strongly recommended for non HHS-funded research (see § 46.103(b)(1)).

What HHS-funded Research Should be Covered by These Regulations and What Research Should be Exempt?

Research Covered by these Regulations

Recommendations of the National Commission:

The Secretary should promulgate regulations governing ethical review of all research involving human subjects that is subject to federal regulation. Furthermore, all research involving human subjects sponsored or conducted by an institution that receives funds from any federal department or agency to conduct health related research shall be reviewed by and conducted in accordance with the determinations of an IRB established and operated in accordance with the regulations. (43 FR 56176)

HHS Proposed Regulations

A significant proportion of the recommendations of the National Commission are essentially implemented, but certain research is specifically exempted. Final authority to determine whether a particular activity is exempt from these regulations rests with the Secretary and thus the Secretary may override an institution's decision, for example, that an activity is exempt. In addition, the Secretary may require that specific research or nonresearch activities or classes of research or nonresearch activities conducted or funded by the Department, but not otherwise covered by these regulations, comply with these regulations, and may also exempt specific activities or classes of activities, otherwise covered by these regulations, from some or all of these regulations. Also, compliance with these regulations in no way renders inapplicable pertinent state or local laws or regulations or other federal laws or regulations. (44 FR 47692-47693)

Public Comment: Fewer than thirty public comments addressed the sections of the HHS proposed regulations summarized above. A few among them were of the opinion that HHS should limit regulations to specific areas of documented abuses rather than promulgate regulations of a broad scope. Other commentators addressed various aspects of the Secretary's authority to regulate research activities. A few

commentators argued for incorporating within the regulations provisions for procedural review of the Secretary's determination whether a particular activity is exempt. Several commentators objected to the provision that the Secretary may require that specific research or nonresearch activities or classes of such activities comply with the proposed regulations, without opportunity for adequate public comment and open deliberation. While no commentators questioned the authority of the Secretary to exempt specific activities or classes of activities, several emphasized the need for the opportunity for public comment should the Secretary exercise this authority. One commentator objected to a confusion in the section relating to the Secretary's authority to determine whether an activity is exempt, on the grounds that the section implied that the Secretary's authority to exempt particular activities extended also to non HHS-funded research.

HHS Response: The HHS proposed regulations closely parallel the recommendations of the National Commission and were issued in fulfilling the mandate of the National Research Act (Public Law 93-348). In developing the HHS proposed regulations care was taken to provide protection for human subjects involved in those activities that present risk to subjects, while exempting from coverage by the regulations many forms of research that do not involve risks or involve only slight or remote risks. Since the purpose of the regulations is to protect the rights and welfare of human research subjects. Limitation to those specific kinds of abuses and unethical practices that have been documented in the past could not assure reasonable protections against other foreseeable harms. The Department believes that effective protection for the rights and welfare of subjects, requires preventive safeguards wherever additional risks associated with the research activities can be reasonably foreseen. In response to those arguing for provision for procedural review of decisions by the Secretary, the Department has in place procedures through which an institution may submit supplementary arguments in opposition to a position taken by the Secretary. However, final authority for determining whether a specific research activity is exempt or not must remain with the Secretary. Similarly the Secretary has authority to require that specific research activities or classes of activities comply with these regulations. However, HHS agrees with the concerns raised by public comment and has

removed the reference to "nonresearch activities" from the final regulations. Decisions of the Secretary regarding the exemption of specific research activities or classes of research activities will be published in the **Federal Register** with opportunity for public comment and careful consideration of substantive issues that are raised. HHS regrets that a typographical error in the paragraph concerning the Secretary's authority to determine whether a particular activity is exempt resulted in the confusion about non HHS-funded research.

HHS Decision: The regulations are applicable to all non-exempt research involving human subjects conducted or funded by HHS. This includes research conducted by Department employees. In negotiating interagency agreements, HHS will determine on a case by case basis whether the regulations shall apply. It also includes research conducted or funded by HHS outside the United States, except that in appropriate circumstances, the Secretary may waive some or all of the requirements of these regulations. The Secretary has final authority to determine whether a particular activity is covered by these regulations and, in regard to specific research activities or classes of research activities, may require compliance with these regulations, or may exempt such activities from coverage. Also, no individual may receive HHS funding for research covered by these regulations unless the individual is affiliated with or sponsored by an institution which assumes responsibility for the research under an assurance agreement with the Department. Lastly, compliance with these regulations will in no way render inapplicable pertinent Federal, State or local laws or regulations. (See § 46.101.)

Research Exempt From These Regulations

Recommendations of the National Commission:

The National Commission confined its discussion of exemptions to the issue of informed consent and recommended that, under certain circumstances, informed consent could be waived (43 FR 56179). Waiver by an IRB of informed consent is discussed in detail below. Types of research mentioned in the National Commission's recommendations form the basis for the HHS proposed exemptions.

HHS Proposed Regulations: The HHS proposed regulations do not address whether or not research which is exempt from these regulations should contain provisions for obtaining informed consent.

The Department has proposed to include a list of exempted categories of

research in the final regulations. Two lists were published in the proposed regulations for public comment. (44 FR 47692-47693)

In addition, the Department requested comment on a proposed requirement that an investigator who intends to conduct research involving human subjects which that investigator judges to be exempt must file a justification for exemption, citing the underlying reasons for claiming exemption.

Public Comment: Nearly 300 commentators specifically addressed the issue of exemptions. The overwhelming majority of those commenting supported the concept of exempting from coverage by these regulations certain no-risk, or very low risk, research. Most commentators believe that the adoption of exemptions will clarify coverage questions, significantly reduce the work load of IRBs, and thus allows IRBs to concentrate on the review of research which involves a greater degree of risk to subjects. Only a few commentators opposed the concept of exemptions. The primary reason given was that an IRB ought to review and rule on the adequacy of protections of subjects in all research conducted or sponsored by the institution. A number of commentators favored exemptions but criticized the approach adopted by HHS in formulating exemptions. One group contended that the HHS failure to exempt all forms of social science research constitutes prior restraint of freedom of inquiry in violation of the First Amendment of the Constitution. Several commentators opposed specific lists of exemptions in favor of language in the regulations that would exempt all research utilizing legally competent subjects if that research involved neither deceit nor intrusion upon the subject's person, nor the denial or withholding of accustomed or necessary resources.

HHS Response: The Department has found that public comment supports the concept of exemptions as a means to reduce the burdens upon the institutions and the IRBs without impairing protections for human subjects.

By exempting a number of types of low or no risk research from coverage under these regulations, and by defining more clearly "human subject" the largest portion of social science research will not be subject to IRB review and approval either because it does not involve human subjects or because it does not present risks to subjects. Moreover, despite some general comments that the regulations would impede social research, the Department has been presented no evidence that

social science research that may present risks to subjects has been unduly hampered by the requirement for IRB review and approval. HHS concludes that continued coverage by the regulations of that social science research which poses risks to subjects is justified.

Although HHS found considerable merit to the suggestion that the regulations should define what is covered rather than list specific exemptions if research were exempted from coverage unless it met the criteria proposed by the commentators, there might be other categories of research involving significant risk that would be inadvertently exempted from coverage. Nonetheless, HHS recognizes that it may have unintentionally included within its coverage description types of research which should be exempted and for this reason § 46.101(e) of the final regulations provides for a waiver which can be used to remedy such situations.

HHS Decision: HHS will exempt certain categories of no-risk or very low risk research involving human subjects. The specific exemptions are discussed in detail below.

Exempted Categories of Research

Of the commentators who addressed the two alternative lists of exempted categories of research, five times as many commentators preferred Alternative A to Alternative B. With the public response in mind, HHS chose Alternative A as the basis upon which to develop a list of exempted categories of research for the final regulations. Therefore, the discussions below include public comment that either addressed Alternative A directly or while addressing Alternative B made suggestions and raised issues that were applicable to Alternative A.

Exemption for Certain Large Scale Evaluation Studies

Public Comment: Nearly all commentators took issue with the terms "on a large scale." The main objection centered on the lack of clarity concerning the intent of the above terms and the coverage of the exemption. Most commentators felt the exemption was vague and suggested a variety of changes.

HHS Response: HHS agrees with public comment and new language in the final regulations is designed to clarify the intent of the Department. Additionally, for the reasons listed in the discussion of informed consent below, this exemption is deleted and provisions for waiver of informed consent are added.

HHS Decision: The exemption is deleted and additional provisions for waiver of informed consent are added. (See § 46.116(c).)

Exemption for Educational Practices

Public Comment: The limited public comment received concerning this exemption was generally favorable but suggested minor changes in wording or requested that certain terminology be defined.

HHS Response: The Department considered the commentators' suggestions and added the word "methods" after "classroom management."

HHS Decision: The following category of research involving human subjects is exempt from coverage under these regulations:

Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Exemption for Research Involving Educational Tests

Public Comment: Fewer than ten commentators specifically addressed this proposed exemption. Some suggested the inclusion of cognitive tests among the types of educational tests. Other commentators questioned whether it was necessary to stipulate that in order to qualify for exemption information must be recorded so that subjects could not be identified. A few felt that additional language should be inserted allowing longitudinal or follow-up studies which require the contact of research subjects.

HHS Response: HHS agrees with the addition of cognitive tests to this exemption and has so worded the final regulation. Also, the word "standard" has been removed in the final regulations to avoid the restriction of the exemption to only standardized tests. "Reasonably" likewise is removed from the final regulations because interpretation of the word is subject to a variety of opinions. HHS disagrees with public comment suggesting removal or alteration of language concerning the identification of subjects because this exemption is designed to permit no-risk or low risk research without requiring all the protections of the regulations. However, the risk is increased when identifiers are introduced and, consequently, the basis for exemption of such research is removed.

HHS Decision: The following category of research involving human subjects is exempt from coverage under these regulations:

Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), if information taken from these sources is recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Exemptions for Survey and Observation Research

Public Comment: Nearly forty commentators addressed the proposed exemption for research involving surveys and observation research. Most of those commenting favored the concept of exempting from the regulations innocuous survey and observation research. However, several commentators suggested a variety of changes be made to the proposed language. One frequently addressed topic was that the exemption for survey research left out interview research. Some commentators requested that HHS change the term "results" to "response" since the first term can refer to the findings of a study and not necessarily to the response of, or interaction with, human subjects. The phrase "sensitive topics" drew significant attention. Most of those commenting felt that it would be difficult if not impossible to expect a uniform or consistent interpretation of this phrase. Many of these commentators suggested that HHS define the phrase or reword the final regulations to include better understood examples. Many commentators felt that the observation of public behavior should be exempt, some commentators qualifying this suggestion to mean that observation research should be exempt so long as it did not involve deception. A number also contended that informed consent may not be needed for observational research. A few commentators addressed topics of public officials and publicly available data within the context of observational studies.

HHS Response: HHS believes that much of the research involving survey and observation techniques entails no risk or very low risk. There is no evidence of adverse consequences from research of this kind carried out in the past, and very little evidence of any risk other than possible breach of confidentiality. For the most part, public comments agreed with this position. HHS endorses the public comment suggesting the inclusion of interviews in the proposed survey research exemption. HHS agrees with comment suggesting the term "response" and has

changed the final regulations accordingly. On the issue of "sensitive topics", the Department has included in the final regulations a description of harms that a subject may incur if responses become known outside the research context. The new language should clarify the intent of HHS to protect human subjects from harms resulting from some kinds of survey and observation research. The proposed exemption for observation research is expanded in the final regulations to include language similar to that in the survey research exemption concerning the issue of identifiable responses when those responses, if they became known outside the research, could be harmful to the subjects. The Department notes that in truly public settings research involving the observation of public behavior is not even defined as research involving human subjects.

The Department disagrees with public comment suggesting that informed consent may not be necessary in observation research. The question of whether informed consent is to be sought is to be judged independently from the requirement for IRB review and approval. Exemptions from coverage under the regulations in no way changes any requirements of other federal, state and local laws or regulations on informed consent. Moreover, many professional ethical codes contain a requirement for informed consent.

HHS Decision: The following categories of research involving human subjects are exempt from coverage under these regulations:

Research involving survey or interview procedures, except where all of the following conditions exist: (if responses are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects, (ii) the subject's responses, if they became known outside the research could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior, such as illegal conduct, drug use, sexual behavior, or use of alcohol. All research involving survey or interview procedures is exempt, without exception, when the respondents are elected or appointed public officials or candidates for public office.

Research involving the observation (including observation by participants) of public behavior, except where all of the following conditions exist: (i) Observations are recorded in such a manner that the human subjects can be

identified, directly or through identifiers linked to the subjects, (ii) the observations recorded about the individual, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior such as illegal conduct, drug use, sexual behavior, or use of alcohol.

Exemption for Collection or Study of Existing Data

Public Comment: Fewer than twenty commentators addressed this proposed exemption. The majority of those who commented favored the proposed exemption. Those who criticized the exemption were concerned with the preservation of confidentiality regarding data, documents, records, and specimens. Some commentators wanted clarification that the exemption was intended to apply only to information that has already been collected in connection with some purpose other than that intended by the proposed research activity. A few commentators suggested that expedited review (discussed below) may be desirable since this exemption might conflict with other laws.

HHS Response: In response to public comment, HHS has included clarifying language in the final regulations. First, HHS agrees with public comment that this exemption applies only to existing information, that is, information previously collected for some other purpose. Second, language has been added to clarify the fact that information taken from public sources is also included in the exemption. HHS is concerned about preservation of the confidentiality of data pertaining to human subjects but feels that other federal, state, and local laws or regulations are sufficient to protect the privacy of individuals and the confidentiality of records in cases where the research uses only existing information. It remains the responsibility of the investigator as well as the institution to ensure that such laws and regulations are observed and that the rights of subjects are protected.

HHS Decision: The following category of research involving human subjects is exempt from coverage under these regulations:

Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the

investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Requirement for Filing Justification for Exemption

Public Comment: Nearly forty commentators responded to the Department's request for comment on this proposed requirement. The number of commentators favoring the requirement was equal to the number opposing. Those in favor argued that it would further protect human subjects. Those opposed pointed out that the requirement, while not necessarily adding to the protection of human subjects, could, in effect, undermine the concept of exempt categories of research by requiring the IRBs to carry out the equivalent of expedited review. Others pointed out that research to be funded by the Department would be reviewed for other purposes during the course of which independent judgment on the appropriateness of a claimed exemption would be obtained. Still others felt that the requirement for filing a justification connoted a lack of trust in investigators that is not warranted.

HHS Response: HHS agrees with the arguments presented by those commentators opposing the proposed requirement for filing justification and has not included it in the final regulations.

HHS Decision: The final regulations will not require that an investigator file a separate justification for exemption, although the appropriateness of a claimed exemption will be evaluated in the case of HHS-funded research on the basis of information contained in the research application. Institutions remain free to adopt any administrative procedures relative to exempt categories of research, if they deem them appropriate.

What Are the Definitions of the Key Terms Used in the Regulations?

The following terms were not the subject of significant public comment and are published in the final regulations essentially as proposed: "Secretary," "Department" or "HHS," "institution," and "legally authorized representative" (see § 46.102).

The following terms received considerable public comment and are discussed in detail below: "research," "human subject," "minimal risk," "certification."

Recommendations of the National Commission

The National Commission defined "research" as a formal investigation

designed to develop or contribute to generalizable knowledge; "human subject" as a person about whom an investigator (professional or student) conducting scientific research obtains (a) data through intervention or interaction with the person, or (b) identifiable private information; and "minimal risk" as that risk of harm or discomfort that is normally encountered in the daily lives, or in the routine medical or psychological examination, of normal persons. (43 FR 56175)

HHS Proposed Regulations

The definitions specified in the recommendations of the National Commission are implemented as follows:

"Research" means a formal investigation designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute "research" for purposes of this part, whether or not they are supported or conducted under a program which is considered research for other purposes. For example, some "demonstration" and "service" programs may include research activities.

"Human subject" means an individual about whom an investigator (whether professional or student) conducting research obtains (a) data through intervention or interaction with the person, or (b) identifiable information.

"Minimal risk" is the probability and magnitude of harm that is normally encountered in the daily lives of healthy individuals, or in the routine medical, dental or psychological examination of healthy individuals. (44 FR 47695)

Public Comment: Twenty-one commentators addressed the definition of "research." While a few commentators favored the proposed definition because it offered flexibility to the IRB, a majority of the twenty-one opposed or raised questions about the definition. Several commentators felt that the definition is too broad and should be restricted to biomedical research. These commentators felt that the definition should not encompass subjects not at risk, social science research, or historical research; and some preferred voluntary application of the regulations to behavioral research. In contrast, a few commentators suggested that the definition should encompass research which is so specific as not to yield generalizable results. One commentator argued that the definition violated the First Amendment or at least academic freedom in the area of biographic research. A few commentators suggested that HHS substitute "systematic" for "formal" in

the definition. in order to include pilot studies of otherwise covered research.

The HHS proposed definition of "human subject" generated less than twenty comments. A minority of those addressing the topic felt that the definition was a much-needed clarification and a definite improvement over current regulations (45 CFR Part 46). However, several commentators argued that the definition was too broad and included human subjects which should not be covered by the regulations. These commentators objected to the inclusion of historical, journalistic, behavioral, social science and biographical fields of research in the definition. In order to clarify the Department's intent to provide a definition in accord with that of the National Commission, additional language from the National Commission's report is included in the regulation. This language makes clear the meaning of "intervention," "interaction" and "identifiable private information." Further, it makes clear that the regulations are applicable only to research involving "living" individuals.

Of the eleven comments addressing the definition of "minimal risk," a few endorsed the definition as an improvement over current regulations (45 CFR Part 46) and felt that it is sufficiently precise for the purpose intended. Some commentators suggested that the proposed definition is too vague and perhaps subject to multiple interpretations on the part of IRBs. Other commentators stated that IRBs would need HHS assistance in interpreting the definition. Others pointed out that the proposed definition should not compare the risks of harm to subjects to the risks encountered in the daily lives of "healthy individuals," and suggested that the definition should be specific to the subject population.

The definition of "certification" was excluded inadvertently in the HHS proposed regulations (44 FR 47695). Public comment pointed out that if certification is to be required, it should be defined.

HHS Response: The HHS definitions of "research," "human subject" and "minimal risk" are discussed below in light of the public comment. The definition of "certification" is published in the final regulations essentially as stated in current regulations (45 CFR Part 46).

The HHS proposed definition of "research" follows closely the recommendations of the National Commission. HHS believes that public concerns that the definitions are too broad will in most cases be met by the

exemptions from the regulations (see § 46.101(b)). The National Commission, although not identifying specific fields of research, clearly intended to include behavioral studies in the recommended definition of "research." HHS agrees with this conclusion and does not believe that the definition of "research" violates the rights of investigators given that the regulations exempt research which offers little or no risk to the rights and welfare of human research subjects, HHS restricts the definition to "generalizable knowledge" because the Department does not intend to include activities such as innovative therapy under the regulations.

HHS agrees with the suggestion that the inclusion of pilot studies within the definition of research should be clarified, and has substituted "systematic" for the word "formal" in the definition.

HHS response to the argument that the definition of "human subject" is too encompassing is similar to that stated above. Many activities and projects will not be reviewed by an IRB because they are in the list of exempted categories of research provided at § 46.101(b). Since public comment indicated that the HHS proposed regulations do not clarify whether the regulations apply only to living individuals. HHS clarifies its intention in the final regulations by including the word "living" within the definition of "human subject." In addition, the National Commission specifically recommended that the definition of "human subject" address identifiable "private" information. HHS has reinserted the term "private" to modify "information." This modification is intended to make it clear that the regulations are only applicable to research which involves intervention or interaction with an individual, or identifiable private information. Examples of what the Department means by "private information" are: (1) Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and (2) information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public. In order to constitute research involving human subjects, private information must be individually identifiable. It is expected that this definition exempts from the regulations nearly all library-based political, literary and historical research, as well as purely observational research in most public contexts, such as behavior on the streets or in crowds.

The HHS definition of "minimal risk" essentially parallels the National Commission's recommended definition. Where the National Commission speaks of "normal persons," HHS in the proposed regulations used the terminology "healthy individuals." In light of the public comments on this, however, HHS has reworded the final regulation to reflect its intention that the risks of harm ordinarily encountered in daily life means those risks encountered in the daily lives of the subjects of the research.

HHS agrees with public comment that "certification" should be defined in the regulations. Therefore, the final regulations contain this definition.

HHS Decision: The final definitions of the terms discussed above are:

- (1) "Research" means a systematic investigation designed to develop or contribute to generalizable knowledge;
- (2) "Human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains (a) data through intervention or interaction with the individual, or (b) identifiable private information. "Intervention" includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. "Interaction" includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects;
- (3) "Minimal risk" means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests; and
- (4) "Certification" means the official notification by the institution to the Department in accordance with the requirements of this part that a project or activity involving human subjects has been reviewed and approved by the IRB

in accordance with the approved assurance on file at HHS. (See § 46.102.)

What Should be the Required Elements of the Assurance Agreement Between HHS and the Institution?

Recommendation of the National Commission

Institutions should be required to submit assurances satisfactory to the Secretary and containing information such as the following to enable accreditation determinations to be made: (1) The names and qualifications of members of the IRB and the process by which members are selected; (2) The resources (for example, meeting rooms, staff, office facilities) that will be devoted to the review function; (3) The general operating procedures of the IRB, and the number and types of proposals that are expected to be reviewed by it; (4) Procedures to assure that all research involving human subjects conducted by or at the institution will be reviewed by an IRB and, if approved, will be conducted in accordance with any restrictions or conditions imposed by the IRB; (5) Review and monitoring procedures and provisions for recordkeeping. (43 FR 56177)

HHS Proposed Regulations

The recommendations of the National Commission are essentially implemented by the proposed regulations which establish the minimum requirements for institutional assurances regarding IRBs. Additionally, the assurance shall be executed by an authorized individual on behalf of the institution. The HHS proposed regulations describe in broad terms the types of assurances as well as specify the minimum requirements in detail for both General Assurances and Special Assurances. Also, the Secretary will evaluate each assurance, taking into consideration the adequacy of the IRB in light of the institution's scope of activities, types of subjects, initial and continuing review procedures and other factors. The Secretary may approve or disapprove an assurance or negotiate an approvable one. (44 FR 47693-47694)

Public Comment: Approximately 100 commentators addressed the sections of the proposed regulations regarding assurances. More than two-thirds of the comments are discussed in other sections of the preamble since the final regulations represent a major reorganization of the section concerning assurances. Some commentators felt the statement in the proposed regulation that the research is to be conducted in accordance with the IRB's determinations subtly implies that the

IRB be responsible for enforcing its determinations. According to these commentators, this would involve an IRB in surveillance and not with ethics and risks. A few commentators favored the requirements for General and Special Assurances as proposed. Some felt that the requirements were unnecessarily detailed and that procedural requirements should be the responsibility of the institution. Several commentators argued that provision of meeting space and sufficient staff to support the IRB were not appropriate elements to be included in the regulations and should be deleted. A few commentators suggested that HHS should provide written procedures for the IRB to follow in reporting unanticipated problems involving risks to subjects. While some commentators thought the part of the proposed regulations dealing with the Secretary's evaluation and disposition of assurances was very reasonable, others argued that the standard for evaluation was loose and could contribute to the imposition of harsher requirements on some institutions. Still others questioned if this standard meant that HHS is empowered to assist an institution to develop procedures in order to comply with the regulations. The establishment of an appeals process was raised by several commentators, who felt that an appeal mechanism allowing an investigator recourse to an IRB disapproval of research was an important but missing item in the issue of assurances.

HHS Response: The final regulations contain one section describing assurances. This section sets forth the minimum requirements for an assurance. Various sections of the HHS proposed regulations concerning assurances that more appropriately dealt with recordkeeping, general applicability or IRB review are moved to those respective sections in the final regulations. This reorganization is consistent with some public comment and makes the HHS regulations consistent with those of the FDA.

Concerning public comment that HHS language implies that the IRB be responsible for enforcing its determinations, the final regulations clarify that the institution is responsible for providing assurance that it will comply with the regulations. All references implying that the IRB enforce its determinations are removed. Concerns about the unnecessary detail in the minimum requirement for General and Special Assurances sections should be alleviated by the more streamlined section on assurances in the final

regulations. Arguments for deleting the requirements for meeting space and sufficient staff for the IRB are not persuasive. The National Commission specifically cited resources such as meeting space and sufficient staff as elements that an institution should include in its assurance to the Secretary. In agreeing with the National Commission, HHS notes that current regulations (45 CFR Part 46) specify that appropriate administrative assistance and support shall be provided for the IRB's functions and that the amended regulations clarify what is already required.

HHS disagrees with the public comments asking for HHS to provide written procedures for IRBs to follow in reporting unanticipated problems. Currently, institutions exercise this responsibility and HHS feels this authority should remain within the institution. Public comments also questioned the process by which the Secretary or appropriate HHS officials would evaluate each assurance. HHS proposed language is very similar to that of the current regulations (45 CFR 46) and no significant problems have been encountered. Additionally, HHS has included in the assurance section, specific wording regarding the protection of human research subjects, regardless of source of funding. This issue is thoroughly addressed above in the discussion of non-HHS-funded research. The National Commission did not recommend a mechanism for appeal from IRB determinations, since it felt that the IRB is the final authority at the institution regarding the ethical acceptability of proposed research involving human subjects. HHS does not rule out the possibility of an institution establishing an appeals process in order to provide a second review of research activities that were disapproved by an IRB. However, under such circumstances, the appellate body established must meet all of the requirements of the regulations, including those specifying membership requirements. The HHS language has also been clarified to allow for the possibility that an institution need not establish its own IRB, but arrange in its assurance to use an IRB established by another institution.

HHS Decision: An assurance agreement shall:

(1) Be provided by each institution engaged in research covered by the regulations and shall demonstrate to the satisfaction of the Secretary, that the institution will comply with the regulations;

(2) Provide that research covered by these regulations will be reviewed,

approved, and subject to continuing review by an IRB;

(3) Contain a statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of subjects;

(4) Designate one or more IRBs for which provisions are made for meeting space and sufficient staff to support the IRBs' functions;

(5) Provide a list of IRB members identified by the requirements contained in § 46.103(b)(3); and

(6) Contain written procedures which the IRB will follow conduct initial and continuing review of research, to determine which projects require more frequent review, to insure prompt reporting to the IRB of proposed changes in a research activity, and to insure prompt reporting to the IRB and to the Secretary of unanticipated problems. (See § 46.103.)

What Should Be the IRB Membership Requirements?

Recommendations of the National Commission

The Secretary should by regulation require that an IRB have at least five competent and experienced members of diverse backgrounds and professions, including at least one member who is not otherwise affiliated with the institution, in order for the IRB to carry out its responsibilities and be accorded respect for its determinations. The expertise of the IRB should be supplemented, when necessary, by the use of consultants. If an IRB regularly reviews research that has an impact on vulnerable subjects, the IRB should include persons who are primarily concerned with the welfare of those subjects (43 FR 56178).

HHS Proposed Regulations

The membership specifications of the National Commission are implemented. Additionally, no IRB may consist entirely of men or entirely of women and no IRB member may participate in the review of any project in which that member has a conflicting interest (44 FR 47695).

Public Comment: Of the twenty-two comments specifically addressing the issue of IRB membership, a majority argued for changes in the requirements.

Several commentators expressed concern about achieving the absolute requirement for diversity in members' racial and cultural backgrounds and thus the ability of the IRB to determine the acceptability of research proposals in light of community attitudes. A number of commentators argued that in certain locales severe recruitment

problems exist. The commentators who opposed the requirement for a member who is not affiliated with, or part of the immediate family of a person who is affiliated with the institution, felt that the requirement demonstrated a lack of confidence in the IRB's ability to be objective and posed additional recruitment difficulties. Several commentators objected to the restriction from participation on the IRB of a member who has a conflicting interest in the research project. A few of these commentators felt that the regulations did not take into account the ability of the IRB to act ethically and objectively and to judge when a conflict of interest is present. Others argued that individual members should be responsible to report a conflict to the IRB. Some commentators felt that the restriction of a member from participation, when an investigator was involved in the selection of that member for the IRB, might mean that the chairperson or senior members of the IRB could seldom review research since their selection may have involved many senior investigators. The inclusion on the IRB of members who represent vulnerable categories of subjects was challenged by only a few commentators, who felt that the decision to include members who are primarily concerned with the welfare of these subjects should be left up to the IRB. Some commentators felt that an IRB reviewing drug studies should have at least one physician member.

HHS Response: The IRB membership requirements published in the proposed regulations are very similar to corresponding requirements in current regulations (45 CFR Part 46) and closely parallel the recommendations of the National Commission. Specifically, the proposed HHS requirement that IRB membership reflect sufficient diversity of racial and cultural backgrounds; professional competence; and the ability to review proposals in terms of applicable law, standards of conduct and community attitudes does not represent a change in Department policy, nor does it diverge from the recommendations of the National Commission. A diverse membership is important and should enhance the IRB's credibility as well as insure a sensitivity to the concerns of both investigators and human research subjects. However, because of varying circumstances, such as geographic location, there is the need for flexibility, so that the institution has the ability to recruit competent IRB members. Public comment indicates that this flexibility, though intended, was not reflected clearly in the proposed

regulations. Therefore, HHS has worded the final regulations to clarify this intention. The proposed HHS requirement that the IRB include a person who is not affiliated with the institution is not a new requirement. It, too, is consistent with both the current regulations (45 CFR Part 46) and the recommendations of the National Commission. The National Commission specifically recommended that a member of the immediate family of a person who is affiliated with the institution should not be appointed to serve as the "unaffiliated" member. HHS feels that the inclusion of a person who has no other relationship with the institution other than membership on the IRB serves to maintain the integrity of the IRB and to promote respect for its advice and counsel. The restriction of a member from participating in the review of research in which that member has a conflicting interest is again similar to the restriction in the current regulations (45 CFR Part 46). Very little controversy has been generated over the years concerning this restriction. HHS does concur, however, with the public comment addressing the additional restriction of an IRB member when the review of research involves an investigator who participated in the member's selection for the IRB. The final regulations eliminate this specific restriction in favor of more general and flexible language. In regard to the comment suggesting that a physician member be required for review of drug studies, HHS agrees that this is a reasonable interpretation of the general requirement for professional competence on the IRB.

HHS Decision: An IRB: (1) Shall consist of at least five members of sufficiently diverse backgrounds, including consideration of racial and cultural backgrounds of members and sensitivity to issues such as community attitudes; (2) shall include persons who are able to ascertain the acceptability of research applications in terms of institutional commitments, applicable law and professional standards; (3) shall include members of both sexes; (4) shall include at least one member whose primary concerns are in nonscientific areas; (5) shall consist of members representing more than one profession; (6) shall include a member who is not affiliated or related to a person who is affiliated with the institution; (7) shall include persons who are primarily concerned with the welfare of vulnerable subjects, if the IRB regularly reviews research that involves vulnerable subjects; (8) may invite individuals with competence in special

areas to assist in the review of complex issues; and (9) may not 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. The regulations authorize each IRB to use consultants to assist in review of complex issues which require expertise not available on the IRB. (See § 46.107.)

What Should Be the General Functions and Operations of an IRB?

Recommendation of the National Commission

Except for research that qualifies for expedited review, all research must be reviewed at a convened meeting of the IRB in which a majority of the members are present. Of those in attendance, approval by a majority is required for research to be approved. The membership should be diverse and include members with nonscientific interests. The IRB should be responsible for conducting continuing review and reporting any serious or continuing noncompliance to institutional officials and the Secretary. (43 FR 46178, 56182)

HHS Proposed Regulations

The requirements recommended by the National Commission are essentially implemented. In addition, at least one member whose primary concerns are in nonscientific areas shall be present at all convened meetings where research is reviewed. The IRB shall follow written procedures: (1) For conducting its initial and continuing review of research; (2) For reporting their decision to the investigator and the institution; (3) for determining which projects require review more often than annually and which projects require verification from sources other than the principal investigator that no material change has occurred; (4) for receiving reports of changes or problems in the research; and (5) for insuring that such problems are promptly reported to the Department. (44 FR 47694-47695)

Public Comment: Approximately forty commentators wrote concerning IRB functions and operations and a majority of them expressed opposition to one or more of the requirements. A few commentators objected to the IRB determining which projects require verification, from sources other than the investigator, that no material change had occurred in some protocols since last review. They thought that this implied a lack of trust in the investigator. On another issue, some commentators felt that only major problems should be reported to the

Department, allowing the institution to handle any minor problems that may arise. The quorum requirements for convened meetings came under attack from many of the commentators. They argued that the requirement that a quorum include one member with nonscientific concerns, could give this individual absolute veto power.

Alternatively, it was suggested that a quorum be composed of members whose background and expertise are appropriate to the particular application in question. Another issue that resulted in a number of comments was the reporting of noncompliance to the Secretary. Many commentators felt that the institution, not the IRB, should be responsible for notifying the Secretary of noncompliance by an investigator. Among those who expressed concern over this requirement, a few felt that any problems of noncompliance should be handled by the institution, while allowing HHS to audit their records.

Most commentators who supported the proposed IRB functions and operations requirements also suggested additions to this part of the regulations. Specifically, a few commentators requested that more detailed procedures be included for dealing with exempted research and expedited review. It was suggested by one commentator that HHS develop written procedures for reporting unanticipated problems which may be harmful. Commentators also expressed support for the requirement of convened meetings: however, one commentator requested a provision be included to permit mail approval on some occasions.

HHS Response: The HHS proposed regulations closely parallel the recommendations of the National Commission, relating to IRB functions and operations. One slight departure is the HHS requirement that the "nonscientific" member be present at all convened meetings where review is conducted, thus providing for the representation of various perspectives during IRB review, and enhancing the protection of human subjects. The public comment indicated concern that this could give an individual member veto power, simply by refusing to attend a meeting. This kind of subversion of the IRB process is not anticipated, but even so, if overall membership is diverse, with more than one "nonscientific" member, this problem should not arise. The proposed regulations require, as do the current regulations, that a majority of the members be present at convened meetings. This should enable a thorough and equitable review, while at the same time not make it difficult to obtain a

quorum. Concerning the requirement for convened meetings, HHS believes that, except where expedited review is authorized, they are necessary and will provide for verbal exchange and debate between members. Review and approval by mail might limit the depth of the review, thus impeding the protection of human subjects.

HHS believes that the guidelines requiring institutions to develop written IRB procedures provide sufficient flexibility for institutions and IRBs. The Department considers it an appropriate requirement that procedures be developed to determine whether there is a need for verification from sources other than the investigators that there has been no material change in certain protocols since their previous review. Verification should be available when, in the opinion of the IRB, verification will provide necessary protections for subjects involved in greater than minimal risk research. Finally, the Department should be notified of problems in research and of any continuing or serious noncompliance because HHS is obligated to examine problems associated with research supported by public funds. This obligation is even greater when questions of noncompliance arise.

HHS Decision: The general functions and operations of an IRB shall be:

- (1) To conduct initial and continuing review of research and report the findings and actions to the investigator and the institution;
- (2) To determine which projects require review more often than annually and which projects need verification from sources, other than the investigators, that no material changes have occurred since previous IRB review;
- (3) To review proposed changes in research activities to insure that changes in approved research, during the period for which IRB approval has already been given, not be initiated without IRB review and approval if the changes would affect human subjects;
- (4) To follow procedures to insure that the IRB and HHS receive reports of unanticipated problems involving risks to subjects and others;
- (5) To conduct its review of research (except where an approved expedited review procedure is used) 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;
- (6) To approve research only with the concurrence of a majority of those members in attendance; and

(7) To report to the institution and HHS any continuing or serious noncompliance, by the investigators, with the requirements and determinations of the IRB. (See § 46.108.)

What Should be the Requirements for IRB Review and Approval of Research?

Recommendation of the National Commission

An IRB should have the authority to review and approve, disapprove, require modification in and conduct continuing review (at least annually) of research involving human subjects conducted at the institution. When appropriate, the IRB should have the authority to suspend approval of research that is not being conducted in accordance with the determinations of the IRB or in which there is unexpected serious harm to subjects. Also as part of its continuing review responsibility, the IRB should have the authority to observe the consent process of the research itself on a sample or routine basis, or have a third party (not associated with the research or investigator) do so. IRB review and approval should be based on affirmative determinations that: (1) The research methods are appropriate to the objectives of the research and field of study; (2) the selection of the subjects is equitable; (3) the risks to subjects are minimized by using the safest procedures consistent with sound research design and, whenever appropriate, by using procedures being performed for diagnostic and treatment purposes; (4) risks to subjects are reasonable in relation to the anticipated benefits to subjects and importance of the knowledge to be gained (the possible long-range effects of applying knowledge gained in the research should not be considered as among those research risks falling within the purview of the IRB.); (5) informed consent will be sought under circumstances that provide sufficient opportunity for subjects to consider whether or not to participate and that minimize the possibility of coercion or undue influence; (6) informed consent will be communicated in language that is understandable to the subject and should be in accordance with certain basic elements of informed consent; and (7) informed consent will be appropriately documented unless it is determined to be unnecessary or inappropriate. The IRB should inform investigators of the basis for its decisions to disapprove or require modification in proposed research and give the investigators an opportunity to respond in person or in writing. (43 FR 56178-56179, 56182)

HHS Proposed Regulations

The review and approval requirements suggested by the National Commission are implemented. In addition, the requirements for continuing review are expanded. The IRB shall promptly report any suspension or termination of approval to the investigator, appropriate institutional officials and the Secretary, including a statement of the reasons for the IRB's actions. The proposed regulations added an additional approval requirement. The IRB shall, where appropriate, require that the research plan make adequate provision for monitoring the data collected to insure the safety of subjects. (44 FR 47695-47696).

Public Comment: Over one-third of the approximately 500 commentators wrote about one or more of the IRB review and approval requirements. Continuing review drew substantial opposition. A few commentators objected to the IRB functioning as a policing body, by requiring it to monitor the consent process. One commentator felt this placed the IRB in a conflict of interest situation, acting as both judge and jury, while another indicated this to be a possible intrusion into the doctor-patient relationship. Continuing review also was noted as being "bureaucratic make-work," placing significant demands on the IRB. A few commentators suggested that more precise criteria be given for continuing review. Strong opposition was voiced, concerning the requirement that IRBs report any suspension or termination of approval to the Secretary; they felt that this is an institutional responsibility. A few commentators thought the procedures for notifying the investigator of the IRB's decision should be deleted from the regulations, and each institution should be allowed to develop its own procedure. The investigator's right to appeal a negative decision was objected to by one commentator.

A majority of the public comments that addressed this issue were specifically directed at one or more of the requirements to be satisfied before approval can be given. Many commentators objected to an IRB determining if the research methods are appropriate to the objectives of the research and field of study. Among these commentators, many argued that the IRB does not have the expertise to make judgments on scientific merit, since it is primarily designed to insure the protection of human subjects. This requirement, some commentators indicated, could subvert academic freedom and possibly stifle innovative

research. The same argument was given in opposition to the requirement that the IRB decide whether the selection of subjects is equitable, taking into account the purpose of the research. The commentators objected further, stating that this would require IRB review of the experimental design, which is not an appropriate responsibility for an IRB. Some commentators questioned the meaning of "equitable," and requested that it be more clearly defined. One commentator felt that the section on equitable selection of subjects should be expanded since it precedes other specific subparts where it is discussed further. The requirement, that risks be minimized by using sound research design and whenever appropriate, by using a procedure already being used on the patient for diagnostic purposes, was again felt by some commentators to be beyond the realm of the IRB's responsibility. They argued that this required the IRB to make judgments it is not qualified to make. One commentator was concerned that, as written, this requirement might curtail research design. Public comment also showed some opposition to the requirement that the IRB insure that the risks to subjects are reasonable in relation to anticipated benefits to subjects and importance of knowledge to be gained. One commentator felt that this required a value judgment, and that a uniform interpretation is not possible from one IRB to another. Another argued that risks can only be assessed in relation to the likely alternative course of action. Some felt the wording of this requirement was vague and obscure, the requirement that the IRB should not consider possible long-range effects of applying knowledge gained in the research as among those research risks which fall within the purview of its responsibility, met opposition. A few commentators felt that this was not clear and should be deleted. The requirement that IRB's insure that, where appropriate, the research plan makes adequate provision for monitoring the data collected to insure the safety of subjects was felt by a few commentators to be ambiguous and meaningless. They requested it be deleted from the regulations.

While most of the public comment was in opposition to one or more of the review and approval requirements, the overall response was positive and a few of the requirements met with an affirmative response. One commentator favored continuing review and suggested that it be carried out every six months. Others favored the provision for an investigator to respond in person or

in writing to a negative IRB decision. A few commentators supported the risk/benefit assessment described in the proposed regulations and agreed that the long-range effects of applying knowledge gained in the research should not be considered.

HHS Response: HHS has adopted the recommendations of the National Commission with regard to the IRB's review and approval requirements. The continuing review procedures is not "make-work," or "policing" since it is important that the IRB remain reasonably informed of the progress of the research to insure the protection of human subjects. Continuing review should be carried out through the use of periodic progress reports, submitted at least annually, but possibly more frequently, at the discretion of the IRB, depending on the risk involved in the research. The precise procedure adopted by the IRB for continuing review without unnecessarily hindering research should be left to the discretion of the IRB. Reporting requirements may vary from a simple annual notification, in the case of research involving little or no risk, to more frequent reporting in cases where the risks are greater. In certain cases, for example, large clinical trials, the IRB may require a special mechanism to carry out regular data and safety monitoring functions. The authority given to the IRB to monitor the consent process should not be construed as a requirement. Instead, HHS expects the IRB to utilize this authority only when it is necessary to insure the protection of subjects. The reporting to the Department of the suspension or termination of research is important since HHS has an obligation to examine problems associated with research supported by public funds, but institutions should, where possible, attempt to resolve any problems that arise. Regarding the guidelines for investigator notification, HHS believes the regulations are sufficiently flexible. HHS does intend that the investigators be clearly informed of the IRB's decision to disapprove or require modification in research. However, the IRB can select the mechanism to accomplish this purpose. The investigators do have a right to respond to a negative decision, however the IRB must finally decide on the ethical acceptability of proposed research involving human subjects.

Some commentators objected to one or more of the requirements to be satisfied before approval is given. In accord with the recommendations of the National Commission, HHS has decided that most of these are essential to the protection of human subjects. However,

the requirement that the IRB review the appropriateness of the scientific methods is withdrawn. HHS feels that this is accomplished through mechanisms such as peer review and need not be addressed by these regulations. Consistent with the National Commission's recommendation for equitable selection of subjects, HHS believes that the proposed involvement of hospitalized patients, other institutionalized persons, or disproportionate numbers of racial or ethnic minorities or persons of low socioeconomic status should be justified. This requirement remains in the final regulations as a condition for approval. Since the number of subjects exposed to risk in research should be no larger than required by considerations of scientific soundness, the IRB should insure that research risks are justified by sound experimental design. However, care should be taken to assure that the size of the subject population is sufficient to yield reliable research results.

HHS believes, as did the National Commission, that information and human materials that are obtained for diagnostic purposes should be used whenever possible, provided this use will not unjustifiably increase the burdens of the ill. This provision is not intended to curtail research design, and will enhance the protection of human subjects. The proposed requirement that a risk/benefit analysis be done by the IRB, is necessary to assure a reasonable relationship between the harms that are risked, and the benefits for the subjects and the gains in knowledge that may reasonably be expected to result from the research. The risk/benefit analysis not only aids the IRB in making its judgment, but should help the IRB to determine whether the information that will be given to the subjects is sufficient for the subjects to determine whether or not to participate. In light of the public comment indicating confusion over this requirement, HHS has clarified its intent in the regulations. HHS advises that in evaluating risks and benefits to subjects, an IRB should consider only those risks and benefits that may result from the conduct of the research and not the possible long-range effects of research on public policy. The National Commission advised that, as the vulnerability of patients increased, it becomes more important to evaluate risks of harm and possible benefits and to require a reasonable relationship between them. Therefore, HHS cautions that, in risk assessment, the IRB should look at the context in which the research is conducted. For example, someone

known to be under physical or emotional duress may be subject to greater risk, as a participant, than someone who is not under duress. In regard to data monitoring, HHS decided that, where appropriate, IRBs shall require that the research plan make adequate provisions for monitoring the data collected, to insure the safety of subjects; this procedure might be an appropriate requirement in large-scale clinical trials. The IRB may require the use of Data Safety Monitoring Boards in order to meet the requirements of this provision. HHS added the requirement that, where appropriate, additional safeguards be taken when vulnerable subjects are involved in the research, because several components of the Department felt that this provision would provide necessary protections where some or all of the subjects are vulnerable to coercion or undue influence.

HHS Decision: In conducting the review of research the IRB shall:

- (1) Review and have authority to approve, require modification in, or disapprove all research activities covered by these regulations;
- (2) Require that information given to subjects as a part of informed consent be in accordance with the requirements of § 46.116 and that additional information be provided to the subjects as deemed necessary by the IRB, to add to the protections of the rights and welfare of subjects;
- (3) Require documentation of informed consent or waive documentation in accordance with § 46.117;
- (4) Notify in writing the investigator and the institution of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the research is disapproved, the investigator shall be given a statement of the reasons for the decision and the opportunity to respond in person or in writing;
- (5) Conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once a year, and have the authority to observe or have a third party observe the consent process and the research (see § 46.109); and
- (6) Have authority to suspend or terminate approval of research that is not in compliance with the IRB's determinations or has been associated with unexpected serious harm to subjects. Any such action shall be reported promptly to the investigator, appropriate institutional officials, and the Secretary, citing the reasons for the IRB's action. (See § 46.113.)

In order to approve research the IRB shall insure that:

- (1) Risks to subjects are minimized by using the safest procedures consistent with sound research design and whenever appropriate, by using procedures already being performed for diagnostic and treatment purposes;
- (2) Risks to subjects are reasonable in relation to anticipated benefits to subjects and the importance of the knowledge that may reasonably be expected to result. When assessing risk the IRB should not consider the possible long-range effects of applying knowledge gained in the research;
- (3) Selection of subjects is equitable, taking into account the purposes of the research;
- (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with § 46.116;
- (5) Informed consent will be appropriately documented in accordance with § 46.117;
- (6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to insure the safety of subjects;
- (7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and
- (8) Additional safeguards are taken when vulnerable subjects are involved in the research, in order to protect against coercion or undue influence. (See § 46.111.)

Should the Regulations Contain a Provision for Expedited Review?

Recommendation of the National Commission

Expedited review should be used by IRBs for categories of research that recur with some regularity, present no more than minimal risk to subjects, and present no serious ethical issue requiring IRB deliberations. This procedure can also be used to review minor changes in previously reviewed research. The IRB chairperson, or an experienced reviewer, designated by the chairperson, should carry out the expedited review. The reviewer should have the authority to approve the research, request modification in the proposal or refer the proposal to the IRB for full review. All IRB members should receive prompt notification of protocols approved by expedited review and any member should be able to request full committee consideration. The IRB's authority to use an expedited review procedure should be revoked if there are

indications that it is being improperly used. (43 FR 56182)

HHS Proposed Regulations

The National Commission's recommendation for an expedited review procedure is essentially implemented, except for the requirements that all IRB members be promptly notified of protocols approved by expedited review and be able to request full committee consideration. The IRB shall describe its expedited review procedure in its General Assurance. (44 FR 47696)

Public Comment: Of the approximately 75 comments addressing expedited review, a majority favored the implementation of this procedure. Expedited review, many commentators agreed, would reduce the burden on the full IRB and enable it to give more thorough consideration to research involving greater than minimal risk. Many commentators felt that the chair person should be able to designate someone other than an IRB member (for example, a staff member), to carry out the expedited review. The suggestion was made, by a few commentators, that a subcommittee of three should be used for expedited review, as opposed to entrusting it to a single individual. Several commentators approved of the procedure, but felt that it needs careful control and the reviewer must be given sufficient information to evaluate the research. One commentator argued that expedited review should be permitted regardless of whether the institution has a General Assurance. There was support for expedited review being used to review minor changes in research, and a few commentators felt that it should also be used for annual reapproval. One commentator, while in favor of expedited review, argued that this was not truly an "expedited" procedure. He suggested that a review procedure was needed that permits the reviewer to apply only those requirements that are appropriate to the particular research project and appropriate to the level of risk.

While the public comment generally demonstrated support for expedited review, there were some commentators who objected to or felt ambivalent about expedited review. A few commentators said that the procedure put too much power in the IRB chairperson. They argued further that all research should receive the same review.

HHS Response: HHS agrees with the National Commission's recommendation that an expedited review procedure be adopted for use by IRBs. Since the public comment demonstrated overall support for the expedited review

procedure described in the proposed regulations, very few modifications were made. HHS realizes that allowing IRB staff members to perform expedited review would alleviate some of the burdens on the IRB. However, unless these individuals become members of the IRB they are not permitted to carry out this review under the requirements of these regulations. Public comment indicated concern over one individual performing expedited review. HHS has included in the regulations the option for an IRB to determine whether one or more individuals should conduct this procedure. HHS has eliminated the distinction between General and Special Assurances in the final regulations.

Consequently, the public comment that an institution should not be required to have a General Assurance in order to conduct expedited review has been addressed. Research subjected to expedited review, however, must still meet all the requirements for approval as described in these regulations. This requirement is implicit but not clearly stated in both the National Commission's recommendations and the proposed regulations. In response to the National Commission's recommendations, HHS decided to require that IRBs adopt a procedure for keeping members advised of research approved under expedited review. Public comment suggested that annual reapprovals, in addition to minor changes in research, be eligible for expedited review. These annual reviews may only be conducted using the expedited review procedure if the proposal meets all of the expedited review requirements.

HHS Decision: Under the provisions for expedited review:

- (1) An IRB may review some or all of the research appearing on the list of Expedited Categories of Research (to be published by the Secretary in the **Federal Register**) through an expedited review procedure, if the research involves no more than minimal risk;
- (2) The IRB may also use expedited review to review minor changes in previously approved research during the period for which approval is authorized;
- (3) The review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among IRB members;
- (4) The reviewers may exercise all of the authorities of the IRB, except they may not disapprove the research;
- (5) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure; and

(6) The Secretary may restrict, suspend, or terminate an institution's or IRB's use of expedited review when necessary to protect the rights or welfare of subjects. (See § 46.110.)

What Categories of Research Should be Eligible for Expedited Review?

Recommendation of the National Commission

Expedited review can be appropriately used for minimal risk research involving the following procedures:

(1) Collection (in a nondisfiguring manner) of hair, nail clippings and deciduous teeth;

(2) Collection for analysis of excreta and external secretions including sweat, saliva, placenta expelled at delivery, umbilical cord blood after the cord is clamped at delivery, and amniotic fluid at the time of artificial rupture of the membranes prior to or during labor;

(3) Recording of data from adults through the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. (These procedures include weighing, electrocardiogram, electroencephalogram, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography.);

(4) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in a six-week period, from subjects 18 years of age and over who are not anemic, pregnant or in a seriously weakened condition;

(5) Collection of both supra- and subgingival plaque, provided the procedure is no more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

(6) Voice recordings made for research purposes such as investigations of speech deficits;

(7) Moderate exercise by healthy volunteers;

(8) The use of survey research instruments (interviews or questionnaires) and psychological tests, interviews and procedures that are part of the standard battery of assessments used by psychologists in diagnostic studies and in the evaluation of judgmental, perceptual, learning and psychomotor processes, provided that the subjects are normal volunteers and that the data will be gathered anonymously or that confidentiality will be protected by procedures appropriate to the sensitivity of the data;

(9) Program evaluation projects that entail no deviation for subjects from the normal requirements of their involvement in the program being evaluated or benefits related to their participation in such programs; and

(10) Research using standard protocols or noninvasive procedures generally accepted as presenting no more than minimal risk, even when done by students. (43 FR 56182)

HHS Proposed Regulations

Except for categories (8) and (10), the National Commission's recommendation is implemented. (44 FR 47696)

Public Comment: Nearly fifty commentators wrote concerning the research categories eligible for expedited review. Among these, a majority suggested changes or additions to the proposed list. Many commentators pointed out that the National Commission's list of expedited review categories was not intended to be comprehensive; but only to serve as an example of the minimal risk activities which could be reviewed using an expedited procedure.

HHS Response: HHS accepted for the most part the list of expedited categories recommended by the National Commission. The category of research involving "program evaluation activities that entail no deviation for subjects from the normal requirements of their involvement in the program being evaluated or benefits related to their participation in such programs," is not included in the final list of expedited categories. This type of research activity is generally exempt from the regulations, if it involves no more than minimal risk to subjects (§ 46.101(b)).

The National Commission recommended that research using survey instruments, psychological tests and interviews in which confidentiality is protected, should receive expedited review, HHS, however, has decided to exempt from the regulations most survey and interview research (§ 46.101(b)).

In addition to the categories listed in the proposed regulations HHS added three other categories of research appropriate for expedited review: (1) Research on individual or group behavior or characteristics of individuals such as studies of perception, cognition, game theory, or test development, where the investigator does not manipulate subjects' behavior and the research will not involve stress to subjects; (2) the study of existing data, documents, records, pathological specimens or diagnostic specimens; and (3) research on drugs or devices for which an investigational new drug exemption or an investigational device

exemption is not required. These three categories of research recur with some regularity, present no more than minimal risk to subjects, and present no serious ethical issue requiring full IRB deliberation.

HHS has decided that the expedited review categories will be, for the present, narrowly defined and limited in number. Once the IRBs have had an opportunity to apply this new technique, and evaluate its adequacy, it may become evident that adjustments in the list should be made. Appropriate revisions to the list will be published in the **Federal Register**.

HHS Decision: The Secretary has published a list of categories of research which may be reviewed by the IRB through an expedited review procedure. The Secretary will amend this list, as appropriate, through republication in the **Federal Register**. The initial list is published in the January 26, 1981 **Federal Register**.

What Should be the Review Responsibilities of the Institution?

Recommendation of the National Commission

Institutions should be required to submit assurances that research will be conducted in accordance with any restrictions or conditions imposed by the IRB. (43 FR 56177)

HHS Proposed Regulations

The HHS proposed regulations do not address specifically the issue of review by the institution.

Public Comment: Several commentators questioned why HHS did not address the review responsibilities of the institution. Specifically, the commentators felt that a statement prohibiting the institution from overruling a disapproval of research by the IRB was erroneously missing from the proposed regulations.

HHS Response: Discussions of assurances and IRB functions and operations above clearly address requirements assumed by the institution regarding the establishment of an IRB for the review and approval of research activities involving human subjects. However, an institution need not conduct or sponsor research that it does not choose to conduct or sponsor, and therefore has final authority to disapprove any research activities approved by the IRB. An institution may not approve research covered by these regulations which has not been approved by an IRB. However, an institution may provide procedures whereby an IRB decision may be appealed to another IRB. The final

regulations take into consideration the public comment and clarify this point in the section dealing with review by institutions.

HHS Decision: An institution:

(1) May review, approve or disapprove research covered by these regulations that has been reviewed and approved by an IRB; and

(2) May not approve research covered by these regulations that has not been approved by an IRB. (See § 46.112.)

What Should be the Requirements of the Regulations Concerning Cooperative Research?

Recommendation of the National Commission

While it is desirable that an institution at which research involving human subjects is conducted establish an IRB, that institution may enter into an agreement with another institution to establish a single IRB or to arrange for review by a neighboring institution's IRB. (43FR56177)

HHS Proposed Regulations

The grantee or prime contractor remains responsible to the Department for safeguarding the rights and welfare of human subjects. When cooperating institutions conduct some or all of the research involving some or all of these subjects, each cooperating institution shall comply with these regulations as though it received support for its participation in the project directly. (44 FR 47698)

Public Comment: Of the ten comments addressing this issue, several were directed toward the conduct of research outside the United States. These commentators disagreed with the requirement that the grantee or prime contractor be responsible for another institution's compliance with the regulations. A few commentators argued that requiring compliance from cooperating institutions is beyond the scope of HHS regulatory authority and that the responsibility should reside entirely within the grantee or prime contractor. A similar number of commentators felt that the HHS proposed regulations regarding cooperative research were more succinct and provided better direction for IRBs than current regulations (45 CFR Part 46).

HHS Response: The IRB review requirements regarding cooperative research activities are very similar to corresponding requirements in current regulations (45 CFR Part 46) and essentially parallel the recommendations of the National Commission. HHS disagrees with the

contention that the responsibility for safeguarding the rights and welfare of subjects should reside only with the grantee or prime contractor. Although the ultimate responsibility is that of the grantee or prime contractor, cooperating institutions share in the responsibility for protecting human subjects. The National Commission specifically stated that institutions should take such steps as are necessary and appropriate to assure compliance by all investigators with IRB requirements and determinations. The requirements in the proposed regulations that the Secretary give approval before joint review or other review arrangements are employed is deleted in the final regulations in order to give the institutions involved in cooperative research projects maximum freedom of discretion while still maintaining adequate protection for the rights and welfare of subjects.

HHS Decision: The requirements involving cooperative research projects are:

(1) In cooperative research projects the grantee or primary contractor remains responsible to the Department for safeguarding the rights and welfare of human subjects; (2) when cooperating institutions conduct some or all of the research involving some or all of these subjects, each cooperating institution shall comply with these regulations as though it received funds for its participation in the project directly; (3) cooperating institutions may use joint review, reliance upon the review of another qualified IRE, or similar arrangements aimed at avoiding duplication of effort. (See § 46.114.)

What Should be the IRB's Recordkeeping Responsibilities?

Recommendation of the National Commission

The IRB should maintain appropriate records, including copies of proposals reviewed, approved consent forms, minutes of IRB meetings, progress reports submitted by investigators, reports of injuries to subjects, and records of continuing review activities. Minutes of IRB meetings should be in sufficient detail to show the basis of actions taken by the IRB. All IRB records should be maintained for five years after completion of the research. (43 FR 56178-56179)

HHS Proposed Regulations

The National Commission recommendations for IRB recordkeeping responsibilities are implemented. In addition, some of the recordkeeping requirements are expanded. The IRB

shall include pertinent information on IRB members in its records. Minutes of IRB meetings shall be in sufficient detail to show attendance at IRB meetings, actions taken by the IRB, the number of members voting for and against these actions, and the basis for the actions (including a written summary of the discussion of substantive issues and their resolution). A copy of any new information provided to the subject during the course of the research shall be retained in the IRB's records. IRB records shall be accessible for inspection by Department representatives and retained for at least five years after completion of the research, or such period as may be specified by program requirements. (44 FR 47694, 47697)

Public Comment: A majority of the 20 public commentators addressing IRB recordkeeping responsibilities were opposed to some aspect of the requirements. Among these, many commentators argued that the maintenance of detailed minutes is inefficient, costly unnecessary, unworkable, and might inhibit discussion. The reference to progress reports, a few commentators argued, should be deleted, since it might be inferred that these are a requirement. One commentator suggested that an institution determine its own policy on IRB recordkeeping responsibilities. A number of commentators questioned the meaning in the regulations of "completion of research," "program" and "new information." A few commentators argued against the five-year requirement for retention of records. Among these, some suggested that a three-year time period be used, thus being consistent with the statutes of limitation in many states. A few commentators argued that the regulations should reflect the confidentiality of IRB records and only allow IRB members, HHS officials and the investigator (into his own file) access to the records. More generally, one commentator objected to IRB recordkeeping responsibilities being a part of the assurance requirements.

HHS Response: The National Commission recommended, and HHS agrees, that it is important to maintain detailed minutes of IRB meetings. However, HHS decided to reduce the burden on IRBs by requiring that the minutes contain: (1) A basis for IRB action only when the research is disapproved, or requires modification and (2) a written summary of the IRB discussion and resolution only when it involves controversial issues. HHS realizes that the maintenance of detailed

minutes could possibly hinder free discussions. These minutes, however, may aid the IRB, institution, or Department in future reviews, or in resolving a problem with the research. The submission of progress reports is essential to the continuing review procedure and will assist the IRB in its continuing review of research. The requirements for IRB recordkeeping responsibilities included in the regulations are consistent with the recommendations of the National Commission. Any additions to the IRB records requirement by HHS, such as a list of IRB members and a copy of the IRB's written procedures are not intended to burden the IRB, but can easily be accomplished by keeping a copy of the institution's assurance agreement on file. In response to public comment indicating confusion about the meaning of "new information," HHS has changed this to "significant new findings." Diverging from the National Commission's recommendations, but consistent with public comment, HHS decided to require that IRB records be retained for at least three years (rather than five) after termination of the last approval period. However, each IRB does have discretion to choose a longer time than three years for record retention. HHS intends that access to IRB records be limited to IRB members. Department officials and investigators (into their own file). HHS requires access to IRB records to properly monitor research conducted with public funds. The question of confidentiality of IRB records is discussed further below. HHS decided to delete the requirement that new information given to subjects, during the course of the research, be reviewed and approved by an IRB. This was an unnecessary burden on the IRB and added no greater protection to human subjects. The reorganization of the regulations resulted in the collection and placement of all IRB recordkeeping responsibilities into a separate section.

HHS Decision: An institution, or where appropriate an IRB, shall maintain adequate records of the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects;

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings, actions taken by the IRB, the number of members voting for and against these actions, and the basis for requiring changes in or disapproving research and

a written summary of the discussion of controverted issues and their resolution;

(3) Records of continuing review activities;

(4) Copies of all correspondence between the IRB and the investigators;

(5) A list of IRB members as required by § 46.103(b)(3);

(6) Written procedures for the IRB as required by § 46.103(b)(4); and

(7) Statements of significant new findings provided to subjects, as required by § 46.116(b)(5).

(b) The records required by this regulation shall be retained for at least three years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Department at reasonable times and in a reasonable manner. (See § 46.115.)

What Should be the Elements of Informed Consent?

Recommendation of the National Commission

The Secretary should require by regulation that all research involving human subjects shall be reviewed by an IRB and that the approval of such research shall be based upon affirmative determinations by the IRB that:

(1) Informed consent will be sought under circumstances that provide sufficient opportunity for subjects to consider whether or not to participate, and that minimize the possibility of coercion or undue influence;

(2) Informed consent will be based upon communicating to subjects, in language they can understand, information that the subjects may reasonably be expected to desire in considering whether or not to participate, generally including:

(a) Notification that participation is voluntary, that refusal to participate will involve no penalties or loss of benefits to which subjects are otherwise entitled, that participation can be terminated at any time, and that the conditions of such termination are stated;

(b) The aims and specific purposes of the research, and whether it includes procedures designed to provide direct benefit;

(c) What will happen to subjects in the research, and what they will be expected to do;

(d) Any reasonably foreseeable risks to subjects, and whether treatment or compensation is available if harm occurs;

(e) Who is conducting the study, who is funding it, and who should be contacted if harm occurs or there are complaints; and

(f) Any additional costs to subjects or third parties that may result from participation.

(3) Informed consent will be documented unless the IRB determines that written consent is not necessary or appropriate because the existence of signed consent forms would place subjects at risk, or the research presents no more than minimal risk and involves no procedures for which written consent is normally required. The National Commission also recommended that there be adequate provisions to protect the privacy of subjects. (43 FR 56179-56182).

HHS Proposed Regulations

The recommendations of the National Commission are essentially implemented. In addition, a statement that new information developed during the course of the research which may relate to the subject's willingness to continue to participate shall be provided to the subject. When appropriate, an IRB shall require additional elements of informed consent such as (1) a statement that the research may involve risks which are currently unforeseeable, (2) a description of when an investigator may terminate a subject's participation without regard to the subject's consent. (44 FR 47696-47697.)

Public Comment: Nearly 100 commentators addressed the issue of the elements of informed consent. The bulk of these commentators expressed general satisfaction with the elements published in the HHS proposed regulations, though many suggested minor changes in content and detail.

Critics made two major points: First, the proposed list is too long, too cumbersome, and out of proportion to harms that have been identified in the past; and second, HHS should retain the list of elements of informed consent required by current regulations.

Specific additional points raised included: (1) The consent procedure need not include information concerning IRB approval of the solicitation of subjects, (2) subjects should be informed when no personal benefit to them is foreseen, (3) the term "new information" should be more specific, (4) compensation and medical treatment availability statements should be deleted and the issue examined more thoroughly, (5) the term "injury" should be replaced by "physical injury."

HHS Response: Most commentators favored the proposed elements of informed consent, but a number felt that some elements could be reworded and combined to clarify and shorten the list. In response, the Department has revised the basic list and moved several

elements to the additional list that an IRB shall require only when appropriate.

Regarding the additional points raised by commentators, HHS responds as follows: (1) HHS agrees with the commentators and has removed this requirement. (2) HHS disagrees because it is implicit in the element requiring disclosure of benefits to be gained that the subject will be informed if no personal benefits are foreseen. (3) HHS agrees with public comment and has inserted new terminology in the final regulations. (4) HHS disagrees with the commentators since the statement has been required by current regulations for nearly two years with no demonstrated ill effect on institutions; however, in response to public comment, the Department has limited the applicability of this requirement to activities involving more than minimal risk to subjects. (5) HHS disagrees because subjects need to consider, in making their decision whether to volunteer for research, what mechanisms, if any, are available for care and what mechanisms, if any, are available for compensation in the event of a research-related injury; the Department sees no reason to limit such disclosure to only one kind of injury.

HHS Decision: Information conveyed in the informed consent procedure shall: (1) Include a reasonable opportunity for the subject to consider participation; (2) be expressed in understandable language; (3) exclude exculpatory language; (4) contain a reasonable explanation of the research, its purposes, procedures, and duration of participation; (5) describe any benefits; (6) describe appropriate alternative procedures; (7) describe the extent to which confidentiality of records will be maintained; (8) explain the availability of compensation and the availability of treatment if injury occurs; (9) contain instructions concerning who may be contacted for answers to pertinent questions; and (10) state the conditions of participation.

Where appropriate one or more of the following elements shall also be provided. The informed consent procedure shall: (1) State that the procedure may involve unforeseeable risks; (2) state circumstances for termination of a subject's participation by the investigator; (3) state possible additional costs to the subject; (4) describe consequences of a subject's withdrawal from participation; (5) state that significant new findings will be provided to the subject; and (6) state the approximate number of subjects in the study.

The IRB may approve a consent procedure which does not include, or

which alters, some or all of the elements of informed consent listed above provided certain conditions are met.

HHS and the National Commission recognize that individuals possess varying degrees of capacity to understand and that a particular individual's capacity can vary from time to time. The final regulations allow for the alteration or waiver of the elements of informed consent, and therefore can serve as a basis for tailoring the amount and complexity of information to be provided in the consent process where potential subjects are likely to have somewhat impaired or limited capacity to understand. Alteration or waiver of consent elements might be approved, for example, for research of no greater than minimal risk involving as subjects persons with chronic or acute mental disabilities, victims of accidents, persons being treated with drugs which impair mental functioning, aged persons with diminished capacity, or persons of limited intelligence. Under these circumstances, these alterations or waivers should only be approved: (1) For use with subjects who are functionally and legally competent to give consent, and (2) if the purpose is to insure that these subjects receive information they can reasonably be expected to understand in order to make a knowledgeable decision regarding their participation in the research. In such cases, the IRB shall insure that procedures are developed to seek consent from subjects at a time when they can make a reasonable judgment, and to determine that each subject has sufficient capacity to give consent.

HHS has proposed that certain large-scale studies be exempt from the regulations, in accord with a notice issued by the Department in 1975 (41 FR 26572). HHS has reconsidered this proposal and feels that IRB review of studies of federal, state, or local benefit or service programs is appropriate even where it may be impracticable to obtain the informed consent of the subject. For example, some projects may be impossible to conduct without affecting all residents of a city, or all beneficiaries of a program, and it is simply impossible to obtain the consent of every person in a large population even if no risks are involved. Therefore, research of this kind will not be exempt from IRB review and approval requirements. However, an IRB may approve the waiver of some or all of the informed consent requirements of these studies. (See § 46.116.)

What Should be the Requirements for Documentation of Informed Consent?

Recommendation of the National Commission

Informed consent should be appropriately documented by the use of written consent forms, and a copy of the consent form given to the subject. When a short form or no written consent is used it is important for the IRB to review the investigator's plans regarding information that is to be provided orally. The IRB may waive the requirement for documentation of consent in the interest of protecting the subjects when a breach of confidentiality may be harmful to them or when the research would be burdened by a requirement for written documentation and the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. (43 FR 56179-56181)

HHS Proposed Regulations

The recommendation of the National Commission is essentially implemented. In addition, when a short form of written consent, indicating that the elements of informed consent have been presented orally to the subject or the subject's legally authorized representative, is used, there must be a written summary of the presentation, signed by those obtaining the consent and by the witness to the oral presentation. Copies of the short form and the summary shall be provided to the subject or the representative. Regarding the IRB waiver of documentation of consent, the subject shall be asked whether the subject wants there to be documentation linking the subject with the research; the subject's wishes will govern. In cases where new information is provided to the subject during the course of the research, this information shall be reviewed and approved by the IRB and a copy of such information retained by the IRB. (44 FR 47697)

Public Comment: Of the fifteen public comments addressing this issue, a few favored the documentation requirements as proposed. Likewise, a few commentators stated that the required documentation was too extensive and exceeded reasonable need. Several commentators addressed the section dealing with the IRB's authority to waive the requirement for the investigator to obtain documentation of informed consent. While some commentators felt that the IRB should not have the authority to waive the requirement, a similar number of commentators agreed with this waiver authority. A few commentators also

questioned the intent and meaning of the terminology "new information" that is provided to the subject during the course of the research.

HHS Response: The proposed requirements for documentation of informed consent are very similar to the documentation requirements in the current regulations (45 CFR 46) and parallel the recommendations of the National Commission. Specifically, the proposed HHS requirements for documentation of informed consent represent a continuance of Department policy regarding this issue. HHS disagrees with the argument that required documentation exceeds reasonable need. HHS also wishes to point out that, in addition to the possibility of a waiver of documentation, a short form of written documentation may be approved by an IRB. Very few public comments addressed this issue, indicating that the existing regulations and the proposed regulations do not pose significant problems regarding documentation of informed consent. Regarding the waiver authority of the IRB, HHS feels that there are convincing arguments raised by the National Commission as well as public comment to maintain this authority within the IRB. One such argument is that the creation of a link between the subject and the research may be harmful to the subject if a breach of confidentiality occurs. However, if the risk of harm, other than that which might arise from breach of confidentiality, is greater than minimal, a waiver may not be issued based on the risk of this breach. The requirement for IRB approval of new information provided to the subject during the course of the research is removed from the final regulations. Information on significant new findings which is given to the subject shall be reported to the IRB, as required by § 46.115.

HHS Decision: Documentation of informed consent;

(1) Shall consist of a written consent form, approved by the IRB, signed by the subject or the subject's legally authorized representative, and a copy given to the person signing the form.

(2) May be a written consent form embodying the elements of informed consent required by § 46.116, which may be read to the subject or the subject's legally authorized representative. The investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(3) May be a short form written consent document stating that the elements of informed consent required by § 46.116 have been presented orally

to the subject or the subject's legally authorized representative. There shall be a witness to the oral presentation. The IRB shall approve a written summary of what is to be said to the subject or the representative. The short form will be signed by the subject or the representative and by the witness. The summary will be signed by the witness and by the person actually obtaining consent of the subject.

(4) May be waived by the IRB if the IRB finds either (i) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or (ii) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.

Where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research. (See § 46.117.)

Should IRBs Review Applications and Proposals Lacking Definite Plans for Involvement of Human Subjects, Before a Grant Award may be Made?

Recommendation of the National Commission

IRB review does not necessarily have to precede application for a grant or contract, although such review should always precede the involvement of human subjects in the research. Review prior to or within a specified time after submission of an application, is most appropriate. (43 FR 56177)

HHS Proposed Regulations

Applications, submitted to the Department without definite plans for involving human subjects, need not be reviewed by an IRB before a grant or contract award may be made. However, no human subjects may be involved in research supported by these awards, until the project has been reviewed and approved by an IRB and certification submitted to the Department. (44 FR 47697)

Public Comment: Eight public comments addressed the issue of research lacking definite plans for involvement of human subjects. Among these a majority favored this addition to the regulations. One commentator requested that "training grants" be

clarified, as "research training grants." A few commentators objected to the requirement that certification of IRB approval be submitted to the Department.

HHS Response: In response to public comment, the word "research" was added to clarify the category of training grants affected, HHS has an obligation to remain informed of any changes in research supported by public funds.

HHS Decision: Applications and proposals submitted to the Department without definite plans for involving human subjects need not be reviewed by an IRB before grant, contract or cooperative agreement funds are awarded. However, except for exempted research, no human subject may be involved in any project supported by these awards until the project has been reviewed and approved by an IRB, as provided in these regulations, and certification submitted to the Department. (See § 46.118.)

What Should be the Investigational New Drug or Medical Device 30-day Delay Requirement?

Recommendation of the National Commission

The National Commission made no specific recommendation on an investigational new drug or device 30-day delay requirement.

HHS Proposed Regulations

Where an institution is required to prepare or submit a certification under these regulations, and an investigational new drug is involved, the drug shall be identified in the certification together with a statement that: (1) The 30-day delay required has elapsed and the FDA has not required that the sponsor continue to withhold or restrict use of the drug in human subjects; or (2) that the FDA has waived the requirement. If the 30-day delay interval has not expired or been waived, a statement shall be forwarded to the Department upon expiration or receipt of a waiver. Certification shall be withheld until such a statement is received. (44 FR 47698)

Public Comment: No significant public comment was received on this issue.

HHS Response: HHS has extended the applicability of this section of the regulations to medical devices which are subject to the Medical Devices Amendments of 1976 (21 CFR 812.3(m)). In addition, this section was rewritten to enhance clarity but without further change in overall substance.

HHS Decision: When an institution is required to prepare or to submit a certification with an application or

proposal covered by these regulations and the application or proposal involves an investigational new drug or a significant risk device, the institution shall:

(1) State whether the 30-day interval required for investigational new drugs or significant risk devices has elapsed, or whether the FDA has waived that requirement;

(2) State whether the FDA has requested that the sponsor continue to withhold or restrict the use of the drug or device in human subjects, if the 30-day delay interval has expired;

(3) Send a statement to the Department upon expiration of the interval, if the 30-day delay interval had not expired or been waived at the time of certification.

The Department will not consider certification acceptable until the institution submits a statement that: (1) The 30-day delay interval has elapsed and FDA has not requested the use of the drug or device limited; or (2) FDA has waived the 30-day interval. (See § 46.121.)

Should HHS be Able to Prematurely Terminate Research Funding and How Should This Affect the Evaluation of Subsequent Applications and Proposals by the Institution?

Recommendation of the National Commission

The National Commission made no specific recommendation on HHS termination of research funding.

HHS Proposed Regulations

If in the judgment of the Secretary an institution is not in compliance with the terms of these regulations, with respect to any particular research project, the Secretary may require the Department to terminate or suspend funding. In making determinations on applications for funding, the Secretary may take into account, in addition to other eligibility requirements, such factors as:

(1) Whether the applicant has been subject to termination or suspension;

(2) Whether the applicant or person responsible for the scientific or technical aspects of the activity has in the judgment of the Secretary failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not Department funds were involved); and

(3) Whether, where past deficiencies have existed in discharging this responsibility, adequate steps have, in the judgment of the Secretary, been taken to eliminate these deficiencies. (44 FR 47698)

Public Comment: Only two commentators addressed the issue of termination and suspension of funding. One of the commentators suggested that the Secretary be required to inform institutions of the reasons for termination, while both argued that HHS should institute a mechanism for appeal.

HHS Response: Upon suspension or termination of funding, Department program requirements insure that the institution affected will receive sufficient documentation of the reasons for this action. The Department already has procedures in place, through which an institution can provide supplemental information in opposition to a position taken by the Secretary. HHS decided to delete from the regulations the requirement that the Secretary consider whether adequate steps had been taken to eliminate any past deficiencies in the protection of human subjects. This was determined to be unnecessary, when the other requirements of this section are considered. The provision was also reworded for purposes of clarity.

HHS Decision: If it is determined that an institution is out of compliance with these regulations, the Secretary may require that the Department terminate or suspend funding for the project, in the manner prescribed in applicable program requirements. In making decisions about funding applications or proposals covered by these regulations the Secretary may take into account, in addition to all other eligibility requirements and program criteria, such factors as:

(1) Whether the applicant has ever had funding for a project suspended or terminated; and

(2) Whether the applicant or the person directing the scientific or technical aspects of the activity has in the judgment of the Secretary materially failed to discharge responsibility for the protection of the rights and welfare of subjects (whether or not Department funds were involved). (See § 46.123.)

Should There Be Direct Compensation and Protections Against Liability for IRB Members?

Recommendation of the National Commission

The IRB should be provided with protection for members in connection with any liability arising out of their performance of duties while serving on the IRB. This protection can be provided in several ways including sovereign immunity, insurance, indemnification by the institution, or specific provisions of state law. The institution should assure that such protection is provided either by law or by means of institutional

arrangements. The National Commission also recommended that federal law should be enacted to provide direct cost funding for IRBs, a portion of which should be used to compensate members. (43 FR 56177-56179)

HHS Proposed Regulations

There is no provision for direct compensation of or liability protection for IRB members.

Public Comment: All of the commentators who addressed the issue of liability protection for IRBs felt that members should assume no personal liability related to their service on an IRB. One commentator argued that decisions concerning compensation of IRB members should be determined by individual institutions.

HHS Response: Although the National Commission recommended that protection be provided for IRB members in connection with any liability arising out of their performance of duties while serving on an IRB, the Department is hesitant to require liability coverage because there is no certainty that feasible mechanisms are available to provide this protection. Furthermore, the Department is unaware of any successful negligence action which has named an IRB member as a defendant. It therefore believes that liability protection would be an unnecessary and costly requirement. The National Commission recommended that federal law be enacted to provide direct compensation for IRB members. However, no federal legislation for this purpose is currently in force or pending. Unless the Congress enacts legislation implementing the National Commission's recommendation, compensation for IRB members will remain an indirect cost item.

HHS Decision: HHS has decided not to address in these regulations the issues of compensation for IRB members or liability protection for IRB members. Institutions are, of course, free to seek legislation or to make institutional arrangements for liability coverage for IRB members.

Should There Be a Requirement for Confidentiality of Subject Records in the Regulations?

Recommendation of the National Commission

The National Commission recommended that the Secretary, HHS, should require by regulation that there are adequate provisions to protect the privacy of subjects and the confidentiality of data. (44 FR 47691)

HHS Proposed Regulations

Except when otherwise provided by federal, state or local law, information in the records or in the possession of an institution acquired in connection with an activity covered by these regulations which refers to or can be identified with a particular subject, may not be disclosed except: (a) With the consent of the subject or his legally authorized representative; or (b) as may be necessary for the Secretary to carry out his responsibilities. (44FR47698)

Public Comment: Fourteen commentators addressed the issues of the privacy of subjects and the confidentiality of information pertaining to them. A majority of those who commented requested deletion or at least modification of this requirement.

HHS Response: The federal government and some states have statutes which provide for the privacy of human subjects and the confidentiality of information pertaining to them. However, few of these laws provide absolute protections. Consequently, it is inappropriate to require institutions to give assurances of privacy and confidentiality which they may not be able to honor in all circumstances.

HHS Decision: The regulations do not have specific requirements describing how personal information must be maintained or to whom it may be disclosed. However, IRBs will be required to determine that, where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data (§ 46.111(a)(7)). Confidentiality provisions should meet reasonable standards for protection of privacy and comply with applicable laws. Reasonable protection might in some instances include legal protection available upon application (such as the immunity from legal process of certain drug and alcohol abuse and mental health research subject data under sec. 303 of the PHS Act). In addition, the informed consent provision of the regulations (§ 46.116) requires disclosure to each subject of the extent to which confidentiality of records identifying the subject will be maintained.

The Following Sections of the Regulations Were not Controversial and Were Adopted as Proposed

Section 46.119 Research Undertaken Without the Intention of Involving Human Subjects.

Section 46.120 Evaluation and Disposition of Applications and Proposals.

Section 46.122 Use of Federal Funds.
Section 46.124 Conditions.

Dated: December 12, 1980.

Julius B. Richmond,
Assistant Secretary for Health and Surgeon General.

Approved: January 13, 1981.

Patricia Roberts Harris,
Secretary.

Accordingly, Part 46 of 45 CFR is amended below by:

§ 46.205 [Amended]

1. Amending § 46.205(b) by changing the reference in the eighth line from “§ 46.115” to “§ 46.120.”

§ 46.304 [Amended]

2. Amending § 46.304 by changing the reference in the second line from “§ 46.106” to “§ 46.107.”

Subparts A and D [Removed]

3. Removing Subparts A and D and adding the following new Subpart A.

Subpart A—Basic HHS Policy for Protection of Human Research Subjects

- Sec.
- 46.101 To what do these regulations apply?
 - 46.102 Definitions.
 - 46.103 Assurances.
 - 46.104 Section reserved.
 - 46.105 Section reserved.
 - 46.106 Section reserved.
 - 46.107 IRB membership.
 - 46.108 IRB functions and operations.
 - 46.109 IRB review of research.
 - 46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
 - 46.111 Criteria for IRB approval of research.
 - 46.112 Review by institution.
 - 46.113 Suspension or termination of IRB approval of research.
 - 46.114 Cooperative research.
 - 46.115 IRB records.
 - 46.116 General requirements for informed consent.
 - 46.117 Documentation of informed consent.
 - 46.118 Applications and proposals lacking definite plans for involvement of human subjects.
 - 46.119 Research undertaken without the intention of involving human subjects.
 - 46.120 Evaluation and disposition of applications and proposals.
 - 46.121 Investigational new drug or device 30-day delay requirement.
 - 46.122 Use of federal funds.
 - 46.123 Early termination of research funding; evaluation of subsequent applications and proposals.
 - 46.124 Conditions.

Authority: 5 U.S.C. 301; sec. 474(a), 88 Stat. 352 (42 U.S.C. 2891–3(a)).

§ 46.101 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving human subjects conducted by the Department of Health

and Human Services or funded in whole or in part by a Department grant, contract, cooperative agreement or fellowship.

(1) This includes research conducted by Department employees, except each Principal Operating Component head may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or funded by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of this section waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from these regulations unless the research is covered by other subparts of this part:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), if information taken from these sources is recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(3) Research involving survey or interview procedures, except where all of the following conditions exist: (if Responses are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects, (ii) the subject's responses, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior, such as illegal conduct, drug use, sexual behavior, or use of alcohol. All research involving survey or interview procedures is exempt, without exception, when the respondents are elected or appointed public officials or candidates for public office.

(4) Research involving the observation (including observation by participants) of public behavior, except where all of the following conditions exist: (i) Observations are recorded in such a

manner that the human subjects can be identified, directly or through identifiers linked to the subjects, (ii) the observations recorded about the individual, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior such as illegal conduct, drug use, sexual behavior, or use of alcohol.

(5) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(c) The Secretary has final authority to determine whether a particular activity is covered by these regulations.

(d) The Secretary may require that specific research activities or classes of research activities conducted or funded by the Department, but not otherwise covered by these regulations, comply with some or all of these regulations.

(e) The Secretary may also waive applicability of these regulations to specific research activities or classes of research activities, otherwise covered by these regulations. Notices of these actions will be published in the **Federal Register** as they occur.

(f) No individual may receive Department funding for research covered by these regulations unless the individual is affiliated with or sponsored by an institution which assumes responsibility for the research under an assurance satisfying the requirements of this part, or the individual makes other arrangements with the Department.

(g) Compliance with these regulations will in no way render inapplicable pertinent federal, state, or local laws or regulations.

(h) Each subpart of these regulations contains a separate section describing to what the subpart applies. Research which is covered by more than one subpart shall comply with all applicable subparts.

§ 46.102 Definitions

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

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

(c) "Institution" means any public or private entity or agency (including federal, state, and other agencies).

(d) "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(e) "Research" means a systematic investigation designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute "research" for purposes of these regulations, whether or not they are supported or funded under a program which is considered research for other purposes. For example, some "demonstration" and "service" programs may include research activities.

(f) "human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. "Intervention" includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. "Interaction" includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) "Minimal risk" means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(h) "Certification" means the official notification by the institution to the Department in accordance with the requirements of this part that a research

project or activity involving human subjects has been reviewed and approved by the Institutional Review Board (IRB) in accordance with the approved assurance on file at HHS. (Certification is required when the research is funded by the Department and not otherwise exempt in accordance with §46.101(b)).

§ 46.103 Assurances.

(a) Each institution engaged in research covered by these regulations shall provide written assurance satisfactory to the Secretary that it will comply with the requirements set forth in these regulations.

(b) The Department will conduct or fund research covered by these regulations only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the Secretary that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. This assurance shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of source of funding. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of these regulations applicable to Department-funded research and is not applicable to any research in an exempt category listed in § 46.101.

(2) Designation of one or more IRBs established in accordance with the requirements of this subpart, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of the 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. Changes in IRB membership shall be reported to the Secretary.¹

¹ Reports should be filed with the Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20205.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; (iii) for insuring prompt reporting to the IRB of proposed changes in a research activity, and for insuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the subject; and (iv) for insuring prompt reporting to the IRB and to the Secretary¹ of unanticipated problems involving risks to subjects or others.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by these regulations, and shall be filed in such form and manner as the Secretary may prescribe.

(d) The Secretary will evaluate all assurances submitted in accordance with these regulations through such officers and employees of the Department and such experts or consultants engaged for this purpose as the Secretary determines to be appropriate. The Secretary's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the Secretary may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The Secretary may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Within 60 days after the date of submission to HHS of an application or proposal, an institution with an approved assurance covering the proposed research shall certify that the application or proposal has been reviewed and approved by the IRB. Other institutions shall certify that the application or proposal has been

approved by the IRB within 30 days after receipt of a request for such a certification from the Department. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

§ 46.104 [Reserved]

§ 46.105 [Reserved]

§ 46.106 [Reserved]

§ 46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members' backgrounds including consideration of the racial and cultural backgrounds of members 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. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, including but not limited to subjects covered by other subparts of this part, the IRB shall include one or more individuals who are primarily concerned with the welfare of these subjects.

(b) No IRB may consist entirely or men or entirely of women, or entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in nonscientific areas; for example: lawyers, ethicists, members of the clergy.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participating 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.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex

issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§ 46.108 IRB functions and operations.

In order to fulfill the requirements of these regulations each IRB shall:

(a) Follow written procedures as provided in § 46.103(b)(4).

(b) Except when an expedited review procedure is used (see § 46.110), review proposed research 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 shall receive the approval of a majority of those members present at the meeting.

(c) Be responsible for reporting to the appropriate institutional officials and the Secretary any serious or continuing noncompliance by investigators with the requirements and determinations of the IRB.

§ 46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 46.116. The IRB may require that information, in addition to that specifically mentioned in § 46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with § 46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

¹ Reports should be filed with the Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20205.

§46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary has established, and published in the **Federal Register**, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the **Federal Register**.

(b) An IRB may review some or all of the research appearing on the list through an expedited review procedure, if the research involves no more than minimal risk. The IRB may also use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized. Under an expedited review procedure, the 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 set forth in § 46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Secretary may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

§ 46.113 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) 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. 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.

(3) 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.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by § 46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by § 46.117.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to insure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged, appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§ 46.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§ 46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Secretary.

§ 46.114 Cooperative research.

Cooperative research projects are those projects, normally supported through grants, contracts, or similar arrangements, which involve institutions

in addition to the grantee or prime contractor (such as a contractor with the grantee, or a subcontractor with the prime contractor). In such instances, the grantee or prime contractor remains responsible to the Department for safeguarding the rights and welfare of human subjects. Also, when cooperating institutions conduct some or all of the research involving some or all of these subjects, each cooperating institution shall comply with these regulations as though it received funds for its participation in the project directly from the Department, except that in complying with these regulations institutions may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

§ 46.115 IRB records.

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members as required by § 46.103(b)(3).

(6) Written procedures for the IRB as required by § 46.103(b)(4).

(7) Statements of significant new findings provided to subjects, as required by § 46.116(b)(5).

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Department at reasonable times and in a reasonable manner.

§ 46.116 General requirements for informed consent.

Except as provided elsewhere in this or other subparts, no investigator may involve a human being as a subject in

research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any 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.

(a) Basic elements of informed consent. Except as provided in paragraph (c) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) 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;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(e) 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;

(7) 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

(8) 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.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research is to be conducted for the purpose of demonstrating or evaluating: (i) Federal, state, or local benefit or service programs which are not themselves research programs, (ii) procedures for obtaining benefits or services under these programs, or (iii) possible changes in or alternatives to these programs or procedures; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirements to obtain informed consent provided the IRB finds and documents 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.

(e) The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

§ 46.117 Documentation of informed consent.

(a) Except as provided in paragraph (e) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A "short form" written consent document stating that the elements of informed consent required by § 46.125 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the "short form."

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from

a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

§ 46.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to the Department with the knowledge that subjects may be involved within the period of funding, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants (including bloc grants) where selection of specific projects is the institution's responsibility; research training grants where the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research described in § 46.101(b), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in these regulations, and certification submitted to the Department.

§ 46.119 Research undertaken without the intention of involving human subjects.

In the event research (conducted or funded by the Department) is undertaken without the intention of involving human subjects, but it is later proposed to use human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in these regulations, a certification submitted to the Department, and final approval given to the proposed change by the Department.

46.120 Evaluation and disposition of applications and proposals.

(a) The Secretary will evaluate all applications and proposals involving human subjects submitted to the Department through such officers and employees of the Department and such experts and consultants as the Secretary

determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the proposed research to the subjects and others, and the importance of the knowledge to be gained.

(b) On the basis of this evaluation, the Secretary may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§ 46.121 Investigational new drug or device 30-day delay requirement.

When an institution is required to prepare or to submit a certification with an application or proposal under these regulations, and the application or proposal involves an investigational new drug (within the meaning of 21 U.S.C. 355(i) or 357(d)) or a significant risk device (as defined in 21 CFR 812.3(m)), the institution shall identify the drug or device in the certification. The institution shall also state whether the 30-day interval required for investigational new drugs by 21 CFR 312.(a) and for significant risk devices by 21 CFR 812.30 has elapsed, or whether the Food and Drug Administration has waived that requirement. If the 30-day interval has expired, the institution shall state whether the Food and Drug Administration has requested that the sponsor continue to withhold or restrict the use of the drug or device in human subjects. If the 30-day interval has not expired, and a waiver has not been received, the institution shall send a statement to the Department upon expiration of the interval. The Department will not consider a certification acceptable until the institution has submitted a statement that the 30-day interval has elapsed, and the Food and Drug Administration has not requested it to limit the use of the drug or device, or that the Food and Drug Administration has waived the 30-day interval.

§ 46.122 Use of Federal funds.

Federal funds administered by the Department may not be expended for research involving human subjects unless the requirements of these regulations, including all subparts of these regulations, have been satisfied.

§ 46.123 Early termination of research funding; evaluation of subsequent applications and proposals.

(a) The Secretary may require that Department funding for any project be terminated or suspended in the manner prescribed in applicable program

requirements, when the Secretary finds an institution has materially failed to comply with the terms of these regulations.

(b) In making decisions about funding applications or proposals covered by these regulations the Secretary may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person who would direct the scientific and technical aspects of an activity has in the judgment of the Secretary materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not Department funds were involved).

§ 46.124 Conditions.

With respect to any research project or any class of research projects the Secretary may impose additional conditions prior to or at the time of funding when in the Secretary's judgment additional conditions are necessary for the protection of human subjects.

[FR Doc 81-2579 Filed 1-23-81; 8:45 am]

BILLING CODE 4110-08-M

**DEPARTMENT OF HEALTH AND
HUMAN SERVICES**

Public Health Service

**Research Activities Which May Be
Reviewed Through Expedited Review
Procedures Set Forth In HHS
Regulations for Protection of Human
Research Subjects**

AGENCY: Department of Health and Human Services.

ACTION: Notice.

SUMMARY: This notice contains a list of research activities which Institutional Review Boards may review through the expedited review procedures set forth in HHS regulations for the protection of human subjects.

EFFECTIVE DATE: This Notice shall become effective on July 27, 1981. Institutions currently conducting or supporting research in accord with General Assurances negotiated with the Department of Health and Human Services (formerly HEW) may continue to do so in accord with conditions of their General Assurance. However these Institutions are permitted and encouraged to apply § 46.110 and the list of research categories, as soon as feasible. They need not wait for the effective date or the negotiation of a new assurance to operate under the new sections cited above. Institutions conducting or supporting research in accord with a Special Assurance negotiated with the Department, shall continue to do so until such time as the assurance terminates.

FOR FURTHER INFORMATION CONTACT: F. William Dommel, Jr., J.D., Assistant Director, office for Protection from Research Risks, National Institutes of Health, 5333 Westbard Avenue, Room 3A18, Bethesda, Maryland 20205, telephone: (301) 496-7163.

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the **Federal Register** the Secretary is publishing final regulations relating to the protection of human subjects in research. The regulations amend Subpart A of 45 CFR Part 46.

Section 46.110 of the new final regulations provides that: "The Secretary will publish in the **Federal Register** a list of categories of research activities, involving no more than minimal risk, that may be reviewed by the Institutional Review Board, through an expedited review procedure * * *". This notice is published in accordance with § 46.110.

Research activities involving no more than minimal risk and in which the only involvement of human subjects will be

in one or more of the following categories (carried out through standard methods) may be reviewed by the Institutional Review Board through the expedited review procedure authorized in § 46.110 of 45 CFR Part 46.

(1) Collection of: hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth if patient care indicates a need for extraction.

(2) Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.

(3) Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays, microwaves).

(4) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an eight-week period and no more often than two times per week, from subjects 18 years of age or older and who are in good health and not pregnant.

(5) Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

(6) Voice recordings made for research purposes such as investigations of speech defects.

(7) Moderate exercise by healthy volunteers.

(8) The study of existing data, documents, records, pathological specimens, or diagnostic specimens.

(9) Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the investigator does not manipulate subjects' behavior and the research will not involve stress to subjects.

(10) Research on drugs or devices for which an investigational new drug

exemption or an investigational device exemption is not required.

Dated: January 14, 1981.

Julius B. Richmond,

Assistant Secretary for Health and Surgeon General.

[FR Doc. 81-2589 Filed 1-23-41 8:45 am]

BILLING CODE 4110-08-M

CORRECTIONS

Accordingly, the following corrections are made in FRDoc. 81-2579, appearing on pages 8366 through 8391 in the Federal Register dated January 26,

1. On page 8366:

(a) Third column, second paragraph, line 3, change "other" to "others". As corrected, the line reads "safeguards for others who may have".

(b) Third column, third paragraph, line 15, change "1979" to "1978". As corrected, the line reads "FDA stated in the August 8, 1978".

(c) Third column, third paragraph, line 20, change "1978" to "1979". As corrected, the line reads "on August 14, 1979 in conjunction with a".

2. On page 8367:

a) Third column, under Conforming Amendments, Line 1, change "E" to "B". As corrected, the line reads "Subparts B and C of 45 CFR 46 are".

(b) Third column, under Major Provisions, third paragraph, line 2, change "or" to "on". As corrected, the line reads "the existing HHS policy on protection of".

3. On page 8368, third column, the paragraph beginning "The Commentators" should not be a new paragraph, nor should those words be in italics. As corrected, lines 30 and 31 should read "research funds. The commentators expressing".

4. On page 8369:

(a) Second column, line 3, change "IRE" to "IRB". As corrected, the line reads 'regardless of source of funding.' IRB'.

(b) Third column, second paragraph, lines 16 and 17, there should be a comma, not a period, between "subjects" and "limitation". As corrected, these two lines read "welfare of human research subjects, limitation to those specific kinds of".

5. On page 8373, second column, second paragraph, line 11, there should be a comma, not a period, between "individuals" and "HHS". As corrected, the line reads "living individuals, HHS clarifies its".

6. On page 8374, first column, under Recommendation of the National Commission, line 14, change "expeced" to "expected". As corrected, the line reads "that are expected to be reviewed by it;".

7. On page 8375, first column, under (6), line 2, insert "to" between "follow" and "conduct". As corrected, the line reads "the IRB will follow to conduct initial and".

8. On page 8377, third column, line 42, change "the" to "The". As corrected, the line reads "requirement was vague and obscure. The".

9. On page 8378, first column, under HHS Response, line 5, change "procedures" to procedure". As corrected, the line reads "continuing review procedure is not".

10. On page 8381, third column, under Public Comment, line 8, insert a comma after the word "costly". As corrected, the line reads "inefficient, costly, unnecessary,".

11. On page 8383, second column, third paragraph, line 8, insert the words "and desirable" between "appropriate" and "even". As corrected, the line reads "or service programs is appropriate and desirable even".

12. On page 8386:

(a) Second column, after the table of contents, under Authority, line 2, the line should read "352 [42 U.S.C. 2891-3(a)]." (i.e., an italicized L, not 2891).

(b) Third column, §46.101(b)(3), line 4, change "Responses" to "responses". As corrected, the line reads "responses are recorded in such a".

(c) Third column, §46.101(b)(4), line 5, change "Observations" to "observations". As corrected, the line reads "observations are recorded in such a".

13. On page 8387, second column, §46.102(f), line 1, change '"human subject"' to '"Human subject"'. As corrected, the line reads '(f) "Human subject" means a living".

14. On page 8388, third column, §46.108(c), line 3, there should be a footnote after the word "Secretary". As corrected the lines reads "the Secretary¹ any serious or continuing".

15. On page 8389:

(a) Second column, §46.113, line 12, there should be a footnote after the word "Secretary." As corrected the line reads "theSecretary¹ ." The accompanying footnote should read "¹ Reports should be filed with the Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20205."

(b) Third column, §46.115(a)(7), line 2, change "rquired" to "required". As corrected, the line reads "findings provided to subjects, as required".