



Institutional Review Board  
Guidelines  
for the  
Protection of Human Participants  
in  
Research

North Dakota State University  
Office of Sponsored Programs Administration  
201K Old Main

**NDSU IRB Guidelines**  
**for the Protection of Human Participants**  
**in Research**

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## INTRODUCTION

Universities, hospitals, and other institutions that conduct federally funded research<sup>1</sup> using humans as research subjects<sup>2</sup>/participants are required by federal law to establish a committee responsible for reviewing such proposed research to ensure that the rights and welfare of the participants are protected. The rules governing human subject research are described in the Code of Federal Regulations (CFR) at 45 CFR 46. A copy of the latest revision to 45 CFR 46 is included in this manual (Appendix C).

To comply with these regulations, North Dakota State University has established the Institutional Review Board for the Protection of Human Participants in Research, “the IRB.” IRB policy includes the minimum guidelines established by the regulations, as well as additional policies for research conducted at NDSU. For example, the regulations require compliance only for projects funded by, or regulated by, federal agencies. NDSU IRB policy requires that all research involving the collection of data from human participants, whether funded or regulated by an external organization or not, must comply with NDSU and federal regulations. This manual includes both university and federal policies and procedures covering human participants in research.

IRB policy also complies with additional regulations that may be required by a specific federal agency (e.g., Food and Drug Administration), when a particular regulation applies to a research project to be funded by that agency. These additional regulations are also included in this manual (Appendix D and Appendix F).

These policies and procedures are considered to be in effect immediately upon approval by authorized University officials and remain in effect and enforceable until otherwise amended or repeated.

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<sup>1</sup>See federal definition for “research” [45 CFR 46.102(d)] in Appendix C.

<sup>2</sup>See federal definition for “subjects” [45 CFR 46.102(f)] in Appendix C.

## **STATEMENT OF PRINCIPLES AND PURPOSE**

Persons conducting research involving human subjects have an ethical as well as professional obligation to ensure the safety, protection, and rights of human subject participants. It is the intent of NDSU, through the IRB and the Office of Sponsored Programs Administration, to assist investigators engaged in human subject research to conduct their research along ethical guidelines reflecting professional as well as community standards. This institution recognizes its duty and obligation to protect the rights and welfare of human subjects in research, regardless of the source of funding.

North Dakota State University has an obligation to ensure that ALL research involving human participants meets regulations established by the United States Code of Federal Regulations (CFR). It is not the intent of the University, the IRB, or the Office of Research Administration to interfere in any way with competent, ethical, and sound research involving human participants in research. It is important for us all to observe the “spirit” as well as the “letter” of these regulations, since how we conduct research involving human participants reflects on our professional, personal, and community commitments to rigorous ethical and scientific standards of conduct.

The future, as always, is uncertain. It is likely that not all possible contingencies have been foreseen or considered in these guidelines and procedures. The IRB strives to deliver the best possible service regarding review of research involving human subjects. To assist in the long-term goal of establishing the means and willingness to assure adequate protection of human participants, the IRB needs the cooperation of the research community of scholars at NDSU.

It is the intent of the IRB to invite input from investigators and interested parties regarding revisions and updates to these guidelines and procedures. When and where possible and appropriate, changes in IRB-related activity will incorporate these recommendations.

Working together, we can develop a streamlined effective system of review and assurance regarding an ethical and professional environment of human participant research.

## **SECTION I**

### **THE IRB: WHAT IT IS AND HOW IT WORKS AT NDSU**

#### **Part A: The Institutional Review Board (IRB)**

##### **1. THE IRB OFFICE**

The IRB at NDSU is administered through the Office of Sponsored Programs Administration, which is headed by the Vice President for Research, Creative Activities and Technology Transfer. The IRB Office is located in 201K Old Main, phone number 701-231-8908. The IRB Office includes an Executive Director and support staff.

The Vice President for Research, Creative Activities, and Technology Transfer appoints the Executive Director, who is a member of the staff in the Office of Sponsored Programs Administration. Responsibilities of the Executive Director include the initial review of all research projects, assignment of projects into appropriate review categories (Exempt Certification, Expedited Review, or Full Board Review), and follow-up to ensure IRB project approval. Other duties include certification that qualified projects are Exempt, organization of IRB meetings, development and distribution of meeting minutes, and coordination of all IRB record keeping activities. The Executive Director may act as Chair for a meeting in the absence of the Chair and Vice Chair.

The Executive Director is not a voting member of the IRB. However, it is permissible, if the committee is one member short of a quorum at a meeting, for the Chair to ask the Executive Director to act as a voting member for that particular meeting and to declare a quorum. The Executive Director should not act as a voting member of the IRB unless it is a temporary appointment, made by the Chair, and necessary to conduct business.

##### **2. COMPOSITION OF THE IRB**

Composition of the NDSU IRB follows the minimum guidelines set forth in the Code of Federal Regulations, 45 CFR 46, as follows:

**45 CFR 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, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. 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, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about the experienced in working with these subjects.**

**(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.**

**(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.**

(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 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.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

### **3. SELECTION, APPOINTMENT, TERMS OF OFFICE OF IRB MEMBERS**

#### **Selection**

*NDSU IRB Members:* Each college, using whatever administrative and electoral procedures are appropriate to that unit, nominates and recommends to the Vice President for Research, Creative Activities, and Technology Transfer a candidate to serve as that college's representative to the IRB.

*Non-NDSU IRB Members:* Are recommended for appointment by the Vice President for Research, Creative Activities, and Technology Transfer, with the advise and consent of a simple majority of IRB members present and voting at the meeting during which such candidates are considered. Non-NDSU IRB member-nominees' names and credentials shall be presented to IRB members not less than 14 days prior to their formal consideration and election.

*Additional Members:* May be added to the IRB at the recommendation of the IRB Chair and the Vice President for Research, Creative Activities and Technology Transfer. The addition of new members will follow the appropriate selection procedures described above.

#### **Appointment**

Faculty appointments to the IRB are not automatic or routine. The Vice President for Research, Creative Activities, and Technology Transfer must approve a nominee and officially appoint said person to serve as college representative to the IRB. Conversely, the Vice President for Research, Creative Activities and Technology Transfer can disapprove the college's recommendation of a nominee and request another nominee of that college's choosing.

Since non-IRB members are nominated by the Vice President for Research, Creative Activities, and Technology Transfer, their appointment to the IRB is automatic upon acceptance by the IRB as detailed above.

The **Chair** of the IRB is a direct appointment of the Vice President for Research, Creative Activities, and Technology Transfer and serves at the request of that office. The Chair must be at least an academic-year appointment member of the NDSU faculty with a degree at the doctoral level. Appointment of Chair is renewable in September of each academic year.

The **Vice Chair** is elected by a majority of those IRB members present and voting at the regular September meeting of the IRB. At least one faculty member of the IRB shall be nominated by any member of the IRB (self-nomination appropriate), followed by a period of time sufficient to allow for consideration and evaluation of candidates. The Vice Chair shall serve in that capacity for a period of one year, at which time re-election occurs or a new Vice Chair is elected.

The Vice Chair shall preside at meetings on those occasions when the Chair is unable to attend an IRB meeting or is an investigator on a research project being reviewed or considered by the IRB. The Vice Chair has all associated responsibilities and obligations of the Chair whenever the Chair is



incapable of serving in that capacity. Except when serving as acting Chair, the Vice Chair shall have the same duties and responsibilities as any IRB member.

In the event that both the Chair and the Vice Chair are unavailable to chair a meeting of the IRB, either the Executive Director of the IRB, or a regular board member previously designated as “substitute Vice Chair” by the Chair and the Vice President for Research, Creative Activities and Technology Transfer, shall act as Chair for the meeting, and has all responsibilities and duties associated with the office of Chair for that meeting. Such temporary status as substitute Vice Chair continues until either the Chair or Vice Chair become available to handle IRB matters.

### **Terms of Office (Tenure)**

Each appointed member of the IRB shall serve a regular term of office of three years. At the expiration of an NDSU member’s term of office, the member’s college Dean shall either re-nominate him/her or offer another candidate. The re-nomination or selection process of an NDSU representative shall occur according to his/her unit’s appropriate administrative procedures. As with “new” members, a re-nomination is subject to the approval of the Vice President for Research, Creative Activities and Technology Transfer.

At the expiration of a non-NDSU member’s term of office, the member may be asked by the Vice President for Research, Creative Activities, and Technology Transfer to serve another term, or another off-campus representative may be appointed.

IRB members completing their term(s) of office may be asked to consider serving an additional two years as an alternate member who may be called upon occasionally to make up a quorum for a particular meeting.

Members of the IRB always have the option of not serving their full term (i.e., resigning). Such vacancies shall be filled according to procedures outlined above for new and re-nominated members.

Representatives of colleges are appointed on a “staggered” basis so that there are always experienced members serving on the board. The original schedule of appointments, approved October 13, 1986, is included in Appendix A. Positions will be filled as vacated, each with a three-year term of office, beginning in September of the year appointed.

## **4. REMOVAL OF IRB MEMBERS BEFORE EXPIRATION OF APPOINTED TERM**

It is unlikely that a member of the IRB shall ever conduct him/herself in a manner that will invite a consideration for a request for removal from the IRB. However, a member of the IRB can be removed from the Board by the following procedures.

**Faculty members** can be removed prior to the expiration of their three-year term with a written request for removal submitted to the Vice President for Research, Creative Activities, and Technology Transfer, stating reasons why such person should no longer serve the university community as an IRB member. Approval of this request by the Vice President for Research, Creative Activities, and Technology Transfer and the Chair of the IRB is required. The removal of a faculty member can only originate at the college level.

**Non-faculty members** of the IRB can be removed with the direct approval of the Vice President for Research, Creative Activities, and Technology Transfer, the Chair of the IRB, and no fewer than three additional members of the IRB.

**The Chair of the IRB** serves at the request of the Vice President for Research, Creative Activities and Technology Transfer, who may present a request for removal to the IRB. The Chair can only be removed from that office by a majority vote of the full IRB. A recommendation for removal cannot be issued directly from anyone other than the Vice President for Research, Creative Activities, and

Technology Transfer. If removed as Chair, that faculty member retains regular IRB membership as a college representative for the duration of his/her term.

## **5. IRB MEETING PROCEDURES**

A regular meeting of the IRB shall occur once a month in those months in which a protocol requiring Full Board review has been submitted. Additional special meetings may be called at the discretion of the Chair. Members shall be informed of regular meetings at least five working days in advance of such meetings. Special meetings may be called with short notice, but such meetings must have the majority of the members of the IRB present, including at least one member whose primary concerns are in non-scientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

Research projects which require review by the full board must be reviewed at a convened meeting in which a quorum (simple majority) of IRB members is present, including at least one member whose primary concerns are in nonscientific areas.

The IRB Chair shall prepare the agenda and direct the meeting accordingly. The following meeting format shall be followed:

1. Call to order
2. Announcements
3. Approval of minutes of previous meeting
4. Old business
5. New business
6. Adjournment

### **Review and Consideration of Protocols**

Whenever possible and desirable, the principal investigator (P.I.) or his/her designee shall be present at that portion of the meeting in which his/her proposal is under consideration, in order to clarify relevant portions of the protocol and project.

Members of the IRB are authorized to ask any questions pertaining to the study in order to reach a conclusion regarding risks, benefits, safety, and protection of human participants.

### **Voting Procedures and Options**

After an adequate period of discussion of the research protocol, the Chair may call for a "motion to consider," at which point any IRB member may move for one of the following:

- |                       |   |
|-----------------------|---|
| APPROVAL:             | protocol and consent form(s) are satisfactory as presented, and investigator may begin research immediately;  |
| CONDITIONAL APPROVAL: | project is not satisfactory as submitted. P.I. must make modifications and/or alterations to protocol and/or consent forms(s) as directed by the IRB. Revisions and modifications to the satisfaction of the IRB Chair (acting on behalf of the IRB) may then result in APPROVAL. |
| DEFERRAL:             | insufficient information to reach any definitive conclusion regarding the protocol. Investigator will be asked to revise the protocol and resubmit for full IRB review at a later meeting.  |

DISAPPROVED:

protocol places subjects at unacceptable risk relative to benefits; research project as designed and described is not suitable for involvement of human participants.

Once the “motion to consider” has been seconded, there will be opportunity for further discussion and clarification. The motion can then be voted upon. If the board is voting by electronic mail, members have 7 calendar days to comment or vote. If a response is not made by a member during that time, it is assumed that their vote is in favor of the motion.

In order for the reviewed research to be approved, it must receive the approval of a majority of those members present. Tied votes are considered not approved, and protocols are returned to the P.I. for alterations and modifications necessary to obtain approval.

In any case, the motion at hand must pass by a simple majority of those present, including one member whose primary concerns are non-scientific.

## **6. MINUTES OF IRB MEETINGS**

The Code of Federal Regulations requires the following minimum information to be included in IRB meeting minutes:

**45 CFR 46.115 (2), IRB Records. Minutes of IRB meetings 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.**

These minutes shall serve as IRB records of full review proceedings. All remarks, commentaries, opinions, and votes of board members are eligible to become part of the official record of the meeting.

## **7. IRB REVIEW OF RESEARCH**

The Code of Federal Regulations requires the following minimum criteria for IRB review of research. NDSU IRB review and approval procedures are covered in more detail beginning on page 25.

**45CFR 46.109 (d), IRB Review of Research. 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.**

**45 CFR 46.109 (e), IRB Review of Research. An IRB shall conduct continuing review of research covered by this policy 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.**

In order to determine that all substantive and relevant changes in protocol and/or consent documents are being reported, and in order to verify compliance with IRB regulations, the IRB shall have the authority to physically inspect any research premises or review non-confidential research documents relating to the protocol and procedures being used in human participant experimentation. Generally, the investigator will be asked to provide copies of relevant and necessary documents for IRB review. Such document requests are in addition to that generated in a project progress report. In most cases, this will only occur when there is an indication that a substantive change is in effect which has not been reported. Failure to comply with such a request for information from the IRB may result in suspension or termination of IRB approval of research.

**45CFR 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 officials, and the (appropriate federal) department or agency head.

**45 CFR 46.112, Review by institution.** Research covered by this policy 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.

## **8. REPORTING REQUIREMENTS TO OHRP**

**45 CFR 46.103 (b)(5), Assuring compliance with this policy – research conducted or supported by any federal department or agency.** (b)...Assurances applicable to federally supported or conducted research shall at a minimum include: (5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the [federal] department or agency head, of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

The IRB will file a report to the National Institutes of Health Office of Human Research Protections (OHRP), of injury and/or other unanticipated risks to subjects or others that occurs on a project supported by, or regulated by, a federal agency that has accepted the common rule on human participant research found at 45 CFR 46. The report, on IRB stationery, and signed by the Chair of the IRB and the Vice President for Research, Creative Activities and Technology Transfer will be filed as soon as possible after the date of occurrence.

The university is required to report to the OHRP any termination of a project due to non-compliance with IRB regulations and directives. Further, such non-compliance is reportable to the federal agency supporting the non-compliant research project.

## **Part B: Project Submission, Review, and Approval**

### **1. PROJECT SUBMISSION**

#### **What Activities Require NDSU IRB Review?**

IRB Review is required for all research involving human participants. NDSU IRB review is necessary for investigations conducted at NDSU facilities by faculty, students, staff, or others associated with NDSU. Furthermore, NDSU IRB review is required for investigations conducted elsewhere by any representative of NDSU.

The federal guidelines adopted by NDSU define “research” as any systematic investigation designed to develop or contribute to generalizable knowledge. Therefore, any investigation designed to generate results that could be published (e.g. in a journal, book, technical report, or disquisition) or presented at a conference is considered to be research. Research conducted with human participants for masters or doctoral theses must receive IRB approval prior to initiation.

Typically, classroom exercises do not meet the IRB’s definition of research, since they do not contribute to generalizable knowledge. Such classroom research exercises do not require IRB review. However, in teaching research methods, instructors should be cognizant of relevant issues such as voluntary participation and confidentiality of information when designing activities involving human subjects. Please note: If an instructor anticipates *possibly* publishing or presenting results from classroom research exercises (thus, “research” as defined above) he/she must file for IRB review prior to initiating the project. IRB approval cannot be granted retroactively.

Finally, if a research project involving human participants derives funding granted or channeled through any NDSU organizational unit, NDSU IRB approval is required.

#### **Who Must Submit Projects for NDSU IRB Review?**

Any investigator affiliated with NDSU who plans to conduct research involving human participants must file a request for review with the NDSU IRB in time to obtain IRB approval before the research begins, and before any contact is made with prospective participants. IRB approval cannot be granted retroactively.

It is the responsibility of the NDSU investigator to seek and obtain any off-campus IRB approvals required. The NDSU IRB will not act on behalf of any investigator to obtain approval from another IRB.

Approval from another IRB does not substitute for NDSU IRB review and approval. However, to avoid duplication of effort, documentation of review and approval by another institution’s qualified IRB will typically be accepted by NDSU. The NDSU IRB Office requires a complete copy of the protocol, consent form(s), and documentation of the originating IRB approval. If, however, it is determined that some aspect of the protocol or consent form(s) does not meet NDSU IRB requirements, the IRB will notify the investigator of the concern and the action needed to resolve the situation.

Some NDSU personnel serve as **professional consultants** (as defined in Section 152:1.3 of the *NDSU Policy Manual*) to off-campus agencies or organizations. Occasionally, such participation involves assisting with design, collection, or analysis of data derived from human participants, or the direct involvement with human participants for the purpose of evaluating a program or service. A faculty or staff member serving as a consultant is responsible for his/her own professional and ethical conduct. As stated in Section 152:1.3 of the *NDSU Policy Manual*, “The University does not assume any responsibility for the professional services rendered during an external professional activity.” NDSU IRB review is not required as long as the results of the research activity are for the benefit of off-campus agencies or organization only and not to be used for any NDSU purposes. However, if IRB review is sought and is not available from another source, the NDSU IRB is willing to serve in that capacity.

If the NDSU investigator expects authorship or similar credit, listing an NDSU affiliation, as a result of collaborative research activity, such research arrangements do require NDSU IRB review. In general, any involvement as an NDSU employee or student in project design, subject recruitment, data collection from human participants, or the handling of identifiable human data requires NDSU IRB review.

**NDSU faculty on leave** who conduct research involving human participants at another institution must obtain review and approval from a legally constituted IRB, usually at the host or research-site institution, with a copy of the documentation forwarded to the NDSU IRB Office.

**NDSU faculty** who wish to **continue** recruiting human participants and/or collecting data from human participants for **a research project begun while at their former institution** must notify the NDSU IRB Office of their active status on the project and provide IRB documentation. If all subject recruitment and data collection from humans for the ongoing research project is completed by the time the faculty member joins NDSU, NDSU IRB review is not necessary; however, use of existing data for a different research project requires NDSU IRB review.

**Researchers from other institutions or organizations**, not affiliated with NDSU in any way, who plan to recruit human research participants from certain segments of the NDSU student, staff, or faculty populations, are not required to obtain formal NDSU IRB approval. However, an **NDSU employee or student who is asked by an outside researcher** to be involved in a recruitment process (e.g. release names, distribute or collect consent forms, or be a contact person ) or in a data collection process (e.g. distribute or collect questionnaires) must obtain NDSU IRB approval.

**Visiting faculty** from another institution who conduct research involving human participants while at NDSU must obtain NDSU IRB approval.

### **When Must Projects be Submitted?**

Investigators should file a request for IRB review well before the planned research is to begin. For exempt projects, allow at least a week for IRB exempt certification. Expedited review takes at least two weeks. If many changes are required to consent forms or protocols, expect three to four weeks to obtain approval from expedited review. Projects to be reviewed by the full board should be submitted to the IRB at least two weeks prior to the next scheduled IRB meeting, which is normally held during the second week of each month. Full Board review of a project could take up to a month from the time the project is initially submitted to the IRB Office until final approval is given. Any changes required to be made the protocol and/or consent form(s) as a result of IRB review will take additional time on the part of the investigator and the IRB. Investigators are strongly encouraged to submit requests for IRB review well in advance of the proposed project start date. For example, if you want to begin recruiting subjects in May, submit your request for IRB review in time for the April IRB meeting, which is normally the second week in April. That will give you at least two to three weeks following IRB review to make revisions and obtain final IRB approval before the project begins in May.

### **Where Must Projects be Submitted?**

Requests for IRB review of research projects should be submitted to the IRB Office, 201K Old Main. The mailing address for requests originating off-campus is: IRB, Office of Sponsored Programs Administration, North Dakota State University, P.O. Box 5756, Fargo, ND 58105-5756.

## **2. IRB REVIEW CATEGORIES**

Research projects submitted to the IRB for approval are screened by staff in the IRB Office and placed in one of three review categories: exempt, expedited review, or full board review. This section describes procedures for submission, review, and approval within each category, including an explanation of the review and approval processes.

### **Exempt Certification**

Research activities involving human participants in which there is minimal or no risk and in which the only involvement of human participants would be in one of the criteria described below may be considered by the IRB Office to be exempt from further IRB review. Projects that qualify for exempt status must, however, receive formal written certification of such exempt status. This certification, which is obtained from the IRB Office, serves as an assurance that the project 1) qualifies for exempt status in accordance with federal regulations, and 2) is designed to ensure that the rights and welfare of human participants are protected. Investigators wishing to obtain exempt certification of a project should complete and submit to the IRB Office, along with appropriate attachments, a "Request for Exempt Certification" form (see Appendix A). Instructions for required attachments are included on the form. Investigators will receive written notification of exempt certification within about five working days from the date the request is received in the IRB Office.

**Exempt project design requirements.** In order to meet criteria for exempt certification, projects must be designed to include certain minimum standards set forth in federal regulations covering human participant research. Of primary importance among these standards is informed consent. The basic elements of **informed consent** (described on pages 36-37 or in 45 CFR 46.102(b)) must be communicated to each prospective subject. This may be accomplished by means of a consent form or by a cover letter or information sheet attached to the questionnaires to be distributed. For telephone surveys or face-to-face interviews, the elements of informed consent may be communicated orally. When the elements of informed consent are to be given orally, the investigator must develop a written script of the oral presentation. The script should be submitted to the IRB Office along with the completed "Request for Exempt Certification" form.

Obtaining the signed consent of subjects participating in exempt research projects is generally not required, although the NDSU IRB reserves the right to require signed consent of participants for certain exempt projects. Nevertheless, it is desirable to obtain signed consent for two reasons: 1) having the documented consent (a signature) of participants in the investigator's possession is good insurance if a problem or question should arise about a participant's involvement; and 2) students who will be involved in human research in their professional careers will undoubtedly be required to obtain signed consent of subjects. Learning the process with university research projects will assist them in becoming familiar with the federal regulations that they will be required to follow later in their careers. When signed consent will be obtained from participants, the required format for consent forms (described on pages 40-42) must be followed, omitting those elements of informed consent that do not apply to the project.

**Criteria for exempt status certification.** As stated in the *Code of Federal Regulations* (45 CFR 46.102(b)), research activities in which the only involvement of human participants will be in one or more of the following categories may be certified by the IRB Office as exempt:

1. **Research conducted in established commonly accepted educational settings, involving normal education practices is exempt, 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), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.<sup>1,2</sup>**
3. **Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public**

behavior that is not exempt under #2 above, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. 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.
5. Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.
5. Taste and food quality evaluation and consumer acceptance studies are exempt (i) when wholesome foods without additives are consumed; or (ii) when a food is consumed that contains a food ingredient at or below the level, and for use found to be safe by the Food and Drug Administration, or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture; or (iii) when a food is consumed that contains an agricultural chemical or environmental contaminant at or below the level found to be safe by the Food and Drug Administration, or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

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\*1 Except as provided in footnote 2 below, research described in category 2 that is supported by federal funds and which involves subjects under the age of 18 cannot be certified as exempt, but must be reviewed by either expedited or full board review procedures. Research described in category 2 that will not be supported by federal funds that involves subjects under the age of 18 can be certified as exempt only when the research subjects are students currently enrolled at NDSU (except as proved in footnote 2 below).

\*2 Research on subjects under the age of 18 which involves observation of public behavior is exempt when the investigator does not participate in the activities being observed.

In determining whether a research project qualifies for exempt status, the following requirements should be considered:

1. If a participant's only involvement in a research project is the completion of survey instruments or interview procedures in which the participant is asked to give his/her "natural" responses to questions, free of any prompting or other interventions, the project will normally be considered exempt.
2. If the investigator attempts to influence or change participants' behavior, perception, or cognition, the project cannot qualify for exempt status.
3. A project does not qualify for exempt status if participants are asked to perform physical tasks.

### **Expedited Review**

Research activities involving no more than minimal risk and in which the only involvement of human participants will be in one or more of the categories described on page 21 may be reviewed by the expedited review procedure. See pages 24-25 to determine minimal risk. Federal regulations give the following requirements for the expedited review procedure:

**45CDR 46.110(b)** An IRB may use the expedited review procedure to review either or both of the following:



**(1) some or all of the research appearing on the list (NDSU IRB Guideline booklet, p. 22) and found by the reviewer(s) to involve no more than minimal risk,**

**(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.**

**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).**

The NDSU IRB supplements the federal regulations with the following policy: All protocols within the Expedited Review category will be reviewed by the Executive Director, as assigned by the IRB Chair, and at least one other IRB member. If a reviewer has concerns about a project, the Executive Director will attempt to resolve the concerns through communication with the investigator. If a reviewer's concerns cannot be resolved to his or her satisfaction, the protocol must be referred to the Full Board for review at a convened meeting.

## **Research Activities Which May Be Reviewed Through Expedited Review Procedures**

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 IRB through the expedited review procedure (*Source: Federal Register, Volume 46, page 8392, January 26, 1981*):

- 1. Collection of: hair and nail clippings in a nondisfiguring manner; deciduous teeth; and permanent teeth if patient care indicates 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 procedure 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 (e.g., 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 2 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.**

**Reporting expedited reviews.** 45CFR 46.110(c) has the following requirement for reporting expedited reviews:

**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.**

The NDSU IRB complies with this requirement by including in the agenda page for each meeting a list of all projects received by the IRB Office since the last meeting, and the manner in which each project was reviewed and approved (i.e., exempt, expedited, or full board review).

**Authorization for expedited review.** NDSU is not authorized to approve federally-funded projects by expedited review. 45 CFR 46.110(d) gives the following statement regarding an institution's authorization to use the expedited review procedure:

**(d) The Department or Agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.**

Institutions not having enough federally funded projects involving human subjects are also assumed to not have sufficient experience to conduct expedited reviews. Accordingly, the NDSU IRB conducts expedited reviews only on those projects that will not be supported by federal funds.

**Number of copies.** Investigators wishing to obtain IRB approval of a non-federally-funded project by the expedited review procedure should submit to the IRB Office, with appropriate attachments, an original and two copies of a completed and signed "Request for Expedited or Full Board Review" form (Appendix A). Appropriate attachments include a project description, consent form(s), copies of survey instruments, advertisements to be sent to the media, or any material to be distributed to subjects. Expedited review and approval normally takes about two weeks. Investigators will be notified in writing of IRB project approval or of any changes that may be required for project approval.

**Project description page limitations.** Some protocols are lengthy (e.g., master's papers, master's theses, doctoral dissertations, grant proposals), and contain information not directly related to IRB approval. The IRB receives many requests each month for a approval of protocols involving human subject research, and there is not time for IRB staff or board members to review lengthy protocols to select out the specific information needed to make a decision regarding IRB approval. For this reason, descriptions of projects that qualify for expedited review must be submitted on no more than three typewritten pages. The format and content for the project descriptions are described in "Request for Expedited or Full Board Review" form (Appendix A). If the three-page project description is a condensation of a more lengthy protocol, investigators may also submit one copy of the full protocol if they feel it contains supplemental information that could be useful to the IRB.

**Informed Consent.** The signed consent of participants is required for all projects that are subject to expedited review. See the following excerpt from the Code of Federal Regulation:

**45 CFR 46.116, General requirements for informed consent.** Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy 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.

Consent forms must include the elements of informed consent described in Section II of this manual (also described in the IRB brochure, “Informed Consent Form Requirements”). Consent forms must be written in the format illustrated beginning on page 43 of this booklet, or in the NDSU IRB booklet, “Informed Consent Form Requirements.” When projects are submitted to the IRB Office for expedited review, the consent form(s) will be reviewed for content and format, along with the project description. Consent form(s) and project descriptions that do not conform to the required format will be returned to the investigator for revision before being distributed to the IRB reviewers.

### **Full Board Review**

Research projects that do not qualify for exempt certification or expedited review must be reviewed by the Full Board at a convening meeting of the IRB. IRB meetings are scheduled for the second week of each month. Projects to be reviewed by Full Board review must be submitted to the IRB Office no later than two weeks prior to the next scheduled IRB meeting.

**Number of copies.** Investigators wishing to obtain IRB approval of a project by the Full Board review procedure should submit to the IRB Office an original and 12 copies of a completed and signed “Request for Expedited or Full Board Review” form (Appendix A), with appropriate attachments. Appropriate attachments include a project description, consent forms, copies of survey instruments, advertisements to be sent to the media, and any material to be distributed to participants.

**Project description page limitations.** Most protocols requiring Full Board review are lengthy and contain a substantial amount of detailed information not specifically required for IRB approval. To expedite the Full Board Review process, investigators should submit an abbreviated project description of no more than three pages, addressing all the points described in the “Request for Expedited or Full Board Review” form. This three-page limit is for the project description only, and does not include other appropriate attachments, such as consent forms, questionnaires, etc. In addition, in cases where the project description is condensed from a larger protocol, three copies of the full protocol should also be submitted.

**Informed Consent.** The signed consent of participants is required for all projects that are subject to Full Board Review. See the following excerpt from the Code of Federal Regulations:

**45 CFR 46.116, General requirements for informed consent.** Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy 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.

Consent forms must include the elements of informed consent found on pages 30-40 of this booklet and be written according to the format illustrated beginning on page 43. The elements of informed consent are also described and the format illustrated in the NDSU IRB booklet, “Informed Consent Form Requirements”. When projects are submitted to the IRB Office for Full Board Review, the project description and consent form(s) will be reviewed for content and format. Project descriptions or consent forms that do not conform to the standard format will be returned to the investigator for revision before being distributed to the IRB members for review.

**Full Board review procedures.** When the IRB Office determines that a project requires Full Board review, the investigator will be notified in writing of the date, time, and location of the IRB review. The investigator will be requested to be present at the portion of the meeting in which his/her protocol will be reviewed. S(he) will be asked to give a short verbal description of the project, and may be asked to answer questions regarding the project. The investigator will then be thanked and dismissed, following which the IRB Chair will call for a “motion to consider” from Board members. Voting procedures and options are described on pages 14-15.

Investigators will be notified of the Board's decision within ten days from the date of review. Such notification will be in the form of a letter from the Executive Director, with a copy to the Chair. The letter will describe any changes to the protocol or consent form(s) that are required for final IRB approval. See additional information on the IRB approval process beginning on page 28.

### **3. THE IRB REVIEW PROCESS**

#### **Criteria for IRB Review of Research**

The Code of Federal Regulations requires the following minimum criteria for IRB approval of research:

##### **45 CFR 46.111, Criteria for IRB approval of research.**

**(a) In order to approve research covered by this policy, 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. \*1**

**(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, and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.**

**(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 Section 116.**

**(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by Section 117.**

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

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

**(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or**

**educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.**

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\*1 Note: While it is not the realm of the NDSU IRB's authority to evaluate the scientific, social, or political worthiness of any research project, issues of project design are an appropriate area of concern. An IRB member must consider "design of experiment" in determining whether a protocol should be approved, if such design either directly or indirectly places the subject at risk and if the design is such that the experiment cannot be expected to yield any statistically or scientifically meaningful data. The IRB does not operate as a "censor" of certain kinds of research. However, if the protocol introduces an element of risk that is not outweighed by direct benefit to participating subjects and the design is so flawed as to create a doubt as to its value as a research inquiry, then an IRB member may consider design in arriving at a decision.

### **Determination of Risk**

The IRB will make a decision based on common sense and sound professional judgment as to whether or not the proposed research places the participant "at risk." A participant is considered to be at risk if he/she is exposed to the possibility of harm, whether physical, psychological, sociological, economic, or other, as a consequence of any activity that goes beyond the application of those established methods necessary to meet his/her needs. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Risk as applicable to federal policy is most obvious in medical or behavioral science research projects involving procedures that may induce a potentially harmful altered physical state or psychological condition. The most obvious examples include invasive procedures, the administration of drugs or radiation, the requirement of strenuous physical exertion, and an intervention that precipitates an emotional disturbance. There are social and behavioral research projects in which, although there may be no immediate risk, procedures may be introduced which constitute a threat to the subject's dignity, right to privacy, or economic welfare. There are also medical and biomedical projects concerned solely with organs, tissues, body fluids, and other materials obtained in the routine performance of medical services, which obviously involve no element of physical risk to the subject, but their use for certain research, training, and service purposes may present psychological, sociological, or legal risks to the subject or authorized representatives. The risk element will also be examined for those studies dependent upon existing information or stored data which may have been obtained for non-research purposes but which, when used in a research context, may present risk to the human participant.

If it is determined that a participant will be placed at risk, the IRB will perform a risk/benefit analysis which involves an assessment of the degree of risk, probability of occurrence, reversibility, and relation to anticipated benefits. The IRB will consider the fact that certain subject populations (e.g., children, pregnant women, prisoners, mentally disabled, physically disabled) may be at greater risk than others.

### **Risk/Benefit Analysis**

1. In research involving a non-therapeutic intervention, the potential of risk to the participant must be outweighed or balanced by the potential benefit to the subject and/or by the knowledge to be gained.
2. In therapeutic research involving more than minimal risk, the potential risk should be outweighed or balanced by the potential benefit to the participant. In addition, the relation of the anticipated benefit to the risk must be at least as favorable to the subject in the non-research context. No participant is allowed to continue in a research protocol if another therapy of proven better quality becomes available to the subject.
3. In research where a standard therapy not a part of the research protocol is employed solely for the benefit of the participant along with additional procedure performed solely for research purposes, the anticipated benefits of the therapy cannot be used to justify exposing participants to the risks associated with the research procedures. Such risks can only be justified in light of the potential benefits of the research procedures.

Conversely, only the risks associated with the research procedures should be used in determining the risk/benefit ratio.

4. In research involving a therapy employed for the potential benefit of a participant suffering from a life-threatening illness, the risk of serious adverse effects may be acceptable providing there are no other therapeutic alternatives available to the subject that offer a more favorable risk/benefit ratio.
5. In research where no direct benefits to the participant are anticipated, the IRB will evaluate whether the risks and/or discomfort presented by procedures performed solely to obtain generalizable knowledge are ethically acceptable.
6. In child research involving greater than minimal risk and no prospect of direct benefit to the participant, the following conditions must be met: (a) the risk represents only a minor increase over minimal risk, (b) the research will likely result in an increase in generalizable knowledge which is of vital importance for the understanding of the subject's disorder, condition, or state of health, **AND** (c) the intervention or procedure presents experiences to the participant that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situation.
7. In research involving pregnant women as participants, one of the following conditions must be met: (a) the purpose of the research is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, **OR** (b) the risk to the fetus is minimal. Only those research procedures that would be acceptable for a fetus going to term may be performed. In addition, whenever there is a potential conflict of interest (e.g., likelihood of abortion or planned abortion), the investigator must not be involved in any decision as to the timing, method, and procedures used to terminate the pregnancy or in the determination of viability of the fetus following the termination of pregnancy.
8. In research involving fetuses in utero, one of the following conditions must be met: (a) the purpose of the research is to meet the health needs of the fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, **OR** (b) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means. Only those research procedures that would be acceptable for a fetus going to term may be performed. In addition, the investigator must not be involved in any decision as to the timing, method, and procedures used to terminate the pregnancy or in the determination of viability of the fetus following the termination of pregnancy.
9. In research involving fetuses ex utero where viability has not been ascertained, one of the following conditions must be met: (a) there is no risk to the fetus imposed by the research, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, **OR** (b) the purpose of the research is to enhance the possibility of survival of the fetus. Once a fetus is determined to be viable it is designated an infant and is, therefore, subject to the federal regulations governing child research.

### **Review of Prospective Participant Population**

The IRB will review the prospective participant population and must be assured that: (a) the participant population and number of participants is appropriate with respect to the nature and goals of the research, and (b) the selection of participants is equitable with regard to the potential risks and benefits.

### **Review of Investigator Qualifications**

The IRB will review investigator qualifications and must be assured that (a) the investigator has the appropriate qualifications and/or licensure to carry out the procedures involving human participants with an acceptable degree of potential risk, and (b) the investigator has adequate facilities and equipment to conduct the research with an acceptable degree of potential risk.

### **Review of Experimental Design and Scientific Merit**

The IRB will review experimental design in order to be assured that the potential risks to the participants are minimized and the potential benefits maximized by using procedures consistent with sound research design.

### **Review of Informed Consent**

The IRB will review the consent procedure and the informed consent form to determine if it conforms to NDSU IRB standards and contains all the appropriate elements of informed consent as required by federal regulations.

## **4. IRB APPROVAL OF RESEARCH**

### **Notification of Findings**

The Code of Federal Regulations 45 CFR 46 gives the following guidelines for IRB approval of research:

**45 CFR 46.109 IRB Review of Research. (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 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.**

In compliance with this regulation, investigators will be notified of the Board's decision within ten days from the date of review. Notification will be in the form of a letter from the Executive Director. The letter will describe any changes to the protocol or consent form that are required for final IRB approval. When the IRB Office receives the appropriate documents (protocol and/or consent forms) with required revisions, final IRB approval can follow without further delay.

If APPROVED, the investigator may begin the proposed research project.

If CONDITIONALLY APPROVED, the investigator will be notified of the specific changes to the protocol and/or consent form necessary to proceed with IRB approval of the research protocol. The Executive Director of the IRB will communicate, in writing, the findings of the IRB and the necessary modifications, if any, to the principle investigator. Until the investigator convincingly demonstrates, in writing, to the IRB that all required changes have been made to the IRB's satisfaction, the project CANNOT begin.

If the investigator does not respond to the IRB's notification of required changes within 30 calendar days of receiving CONDITIONAL APPROVAL, the proposed project must be resubmitted for full review again.

The letter of notification to the investigator will convey these stipulations and time limit.

If DEFERRED, the investigator will be notified in writing that the project as described provides insufficient information to reach a decision for approval or disapproval. The investigator will be asked to resubmit for a later regularly scheduled meeting. In addition, the findings of the IRB that resulted in the decision to defer the project will be conveyed in writing to the investigator.

If DISAPPROVED, the reasons for disapproval will be conveyed in writing to the investigator.



**Approval period.** Approval is for a maximum of one year. Multiple-year projects must be reviewed at least annually. See Investigator Reporting Requirements, page 31, for details.

**Certification for Federal Funding.** If an investigator intends to submit an IRB-approved protocol to a federal agency for funding, he/she should inform the IRB Office. The IRB Executive Director will follow that agency's procedures for notifying them of IRB approval of the project.

When a proposal involving the use of human subjects is funded by the National Institutes of Health (NIH), the awarding NIH institute will notify the Office for Human Research Protections (OHRP) that an Assurance of Compliance is needed from the grantee institution (e.g., NDSU). OHRP will contact either the principal investigator or the Office of Sponsored Programs Administration (usually in writing) and request the Assurance. The Assurance of Compliance is completed by the IRB Office on forms provided by OHRP and is submitted to OHRP. The grant will not be awarded until OHRP has received and approved the Assurance of Compliance. OHRP will notify the awarding NIH institute of such approval.

## **Part C: Investigator Reporting Requirements**

NDSU IRB policy requires the following written reports from investigators conducting IRB-approved research: (1) project progress reports, (2) requests for change in protocol/consent form(s), (3) reports of injury/unanticipated events, and (4) project completion reports.

1. Project Progress Reports. Following is an excerpt from the U.S. Code of Federal Regulations:

**45 CFR 46.109(e), IRB Review of Research. An IRB shall conduct continuing review of research covered by this policy 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.**

All non-exempt research projects involving human participants are approved for a maximum of one year at a time. Any project that will not be completed within 12 months of the original IRB approval date must be reviewed by the IRB by the first anniversary of the original IRB approval date in order to receive IRB approval for a second year or portion thereof. When projects are completed in less than one year from the original IRB approval date, the investigator should submit a "Project Completion Report" as soon as the research portion of the project is completed (Appendix A).

A Project Progress/Completion Report reminder is mailed from the IRB Office to an investigator at least one month prior to the anniversary date of his/her project. When it is received in the IRB Office, the annual update will be scheduled for review. Research work will be allowed to continue on a project during the review period unless information contained in the project progress report indicates possible increased risk to subjects, in which case, the IRB Office will request that the research be suspended until the project has been reviewed and approved by the Full Board.

In months in which no meeting is scheduled, the Executive Director may give a project interim approval if the project progress report indicates that there were no problems during the previous year that could have resulted in increased risk to participants. The interim approval will allow the project to continue until the next IRB meeting.

IRB approval of a project progress report is effective for an amount of time, no longer than 12 months, determined by the reviewers. This period will end on the day of the month of the original IRB project approval. For example, a project originally approved on June 23, 1994, must submit a "Project Progress/Completion Report" form for approval no later than June 23, 1995 if the project will continue beyond that date.

### **Format**

Project Progress/Completion Reports should be submitted to the IRB Office, typed on no more than two pages, and attached to a completed and signed "Project Progress/Completion Report" form (Appendix A). The report should include, at minimum:

- the number of participants initiated into the research project during the period being reported;
- a description of the experiences of the participants (benefits, adverse reactions, withdrawals from the research);
- the results of the research thus far;
- a current assessment of the risks and benefits based on study results;
- any new information that has come to light since the IRB's last review;
- a copy of the current "Informed Consent Form."

Occasionally, selected projects will be reviewed more often than annually. Such projects are:

- any research involving fetuses;

- any research involving human participants for which there have been reports of injury or unanticipated problems as a consequence of participating in the research;
- any research for which the IRB had specifically required “more often than annual” review at the time approval was granted;
- any research project the IRB deems appropriate to review on a more-often-than-annual basis, including projects not in any of the above categories.

“More-often-than-annual” reviews will follow the same reporting and review procedures as indicated for project progress reports, with the appropriate changes in reporting intervals and deadlines.

### **Failure to file a project progress/completion report**

If no report is filed within a 30 day period from the anniversary of the original approval date, the investigator will be notified in writing that the approval for the indicated research project has expired. The investigator is prohibited from further experimentation involving human subjects in that research project. This termination notice will be signed by the Chair of the IRB and the Vice President for Research, Creative Activities, and Technology Transfer. Termination is effective from the date of the written notification. In order to re-establish that research project, the investigator must file a new and complete “Request for Expedited or Full Board Review” form, which will be reviewed by the IRB according to the procedure defined by federal regulations.

2. Changes in Protocol/Consent Form(s). Any proposed change in protocol which affects human participants must be reviewed and approved by the IRB prior to implementation, except where an immediate change is necessary to eliminate hazard to the participant. The request for change should be submitted to the IRB Office, typed on no more than two pages, and should be attached to a completed and signed “Request for Change in Protocol/Consent Form(s) Approval” (Appendix A), along with a copy of the revised protocol or consent form.

The request for approval of changes should include:

- (1) a description of the proposed changes;
- (2) justification for the proposed changes;
- (3) any additional comments you wish to make relative to the proposed changes;
- (4) revised consent form(s) when appropriate.

Changes will be reviewed initially by the IRB Office. The investigator will be notified by the IRB Office whether the changes must be reviewed by Full Board Review, Expedited Review, or whether they qualify for Exempt Certification. Appropriate steps will be taken in the IRB Office to ensure a timely review and approval of the changes.

Note: A protocol may be changed without prior IRB approval where necessary to eliminate apparent immediate hazards to the participants or others. However, the IRB must be notified IN WRITING within 72 hours of any change, and IRB review is still eventually required.

3. Report of Injury/Unanticipated Events. Any research-related injuries (physical or psychological), adverse reactions, or unanticipated problems involving subjects or others during the course of an IRB-approved project must be reported in writing to the IRB Office within 72 hours of the occurrence. The report should be a written description of the injury or other event, attached to a completed and signed “Report of Injury/Unanticipated Events” form (Appendix A). Investigators are also strongly encouraged to share such information with their Department Chair and College Dean.

Investigators are encouraged to use their best judgment regarding the nature and degree of a reportable injury or unanticipated problem. In general, anything serious enough to warrant medical or psychiatric intervention is reportable, as are verbal or written complaints of participants in which they proclaim that participation presents substantial discomfort, risk, and/or endangerment beyond that explained to them, or as otherwise stated in the consent form.

When injury or other unanticipated problems occur in projects funded by a federal agency, such event must be reported by the IRB Office to the National Institutes of Health Office for Human Research Protections. See procedures for IRB reports to OHRP, page 16.

## **Part D: Guidelines for Special Types of Research**

1. Research Involving Investigational Drugs. An investigational drug may be defined by one of the following:

- a. a drug in any of the clinical stages of evaluation (Phase I, II, III) which has not been released by the FDA for general use or cleared for sale in interstate commerce;
- b. any commercially available drug proposed for a new use;
- c. any commercially available drug to be used in a new dosage, form, or method of administration;
- d. any commercially available drug which contains a new component such as an excipient, coating, or menstruum;
- e. a new combination of two or more commercially available drugs;
- f. a combination of commercially available drugs in new proportions;
- g. any commercially available drug involved in a post-marketing surveillance.

Good medical practice and patient interests require that physicians be free to use commercially available drugs according to their best knowledge and judgment. If a physician uses a drug for an indication not in the approved labeling, he or she has the responsibility to be well informed about the drug and to base its use on a firm scientific rationale and on sound medical evidence, and to maintain records of the drug's use and effects. Use of a drug in this manner as part of the "practice of medicine" does not require review by the IRB or FDA notification despite the fact that the drug is technically classified as investigational.

The *investigational* use of an approved, marketed product differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a study protocol. When the principal intent of the investigational use of a drug is to develop information about its safety or efficacy, IRB review and approval is required.

When a marketed drug is shipped in interstate commerce for the purpose of conducting a clinical trial on the drug for an unapproved use, at an unapproved dosage, by an unapproved route of administration, or in an altered dosage form, the submission of an Investigational New Drug permit (IND) is required. Even though the law may not require an IND in all investigational situations. The FDA believes that it is in the interests of the investigator and the public for one to be submitted. It is possible that the FDA may have safety data that are not available to the investigator. Furthermore, information obtained from such a clinical trial might expedite either approval of this new use or a decision regarding its abandonment if similar trials showed adverse results or lack of efficacy.

When a marketed drug is shipped in interstate commerce for the purpose of routine clinical use and is subsequently proposed for use in a manner as defined by "investigational drugs," an IND is not legally required, but IRB review and approval must be obtained.

2. Research Involving Medical Devices. Investigational devices are medical devices that are the object of clinical research determining their safety or effectiveness. Studies done to develop safe and effective data for medical devices involving human participants must be conducted according to the requirement of the Investigational Device Exemption (IDE) regulations (21 CFR 812).

Investigational devices are determined to be either significant risk or non-significant risk devices. Examples of non-significant risk devices are: most daily wear contact lenses, lens solutions, heel cups, anti-bacterial surgical garments, incontinent devices, oral training splints, ultrasonic tooth cleaners, and Foley catheters. Investigations of non-significant risk devices must meet the abbreviated IDE requirements. Unless otherwise notified by FDA, an investigation of a non-significant risk device is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements of the IDE regulations. These regulations require, in part, that IRB approval be

obtained and maintained throughout the investigation and that informed consent be obtained and documented.

A significant risk device is one that presents the potential for serious risk to health, safety, or welfare of the participant. Such a device is intended as an implant, is to be used in supporting or sustaining human life, or is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health. Examples of significant risk devices are pacemakers, IUDs, some laser systems, and some hemodialyses systems. Investigations involving significant risk devices must meet the full IDE requirements including the submission of an IDE application to the FDA, and FDA approval of the investigation. As with non-significant risk devices, IRB approval is required prior to conducting clinical trials of the investigational device.

In addition to determining whether a study should be approved, the IRB will also determine whether the device presents significant or non-significant risk. The determination that a device presents non-significant or significant risk is initially made by the sponsor. The proposed study is then submitted to the IRB for review. The IRB may ask for and obtain certain information prior to determining the risk status of the device. A risk assessment determination and the rationale of the sponsor's decision should be provided by the sponsor. The IRB may ask the sponsor whether other IRBs have reviewed the proposed study and what determination was made. The sponsor should notify the IRB of the FDA's assessment of the device's risk if such an assessment has been made. The IRB may also consult the FDA for its opinion.

In deciding if a device presents significant or non-significant risks, the IRB will consider the device's total risks, not as compared with the risks of alternative devices or procedures. If the device is used in conjunction with a procedure involving risk, the IRB will consider the risks of the procedure in conjunction with the risk of the device. The IRB may choose to agree or disagree with the sponsor's initial determination of degree or risk. Sponsors must notify the FDA when an IRB determines that a device, judged by the sponsor not to present a significant risk, should be categorized as a significant risk device.

Once a decision on the degree of risk is reached, the IRB will consider whether the study should be approved or not. Some studies involving non-significant devices may also be considered minimal risk studies and thus may be reviewed through the expedited review procedure established by the IRB. The FDA considers studies of all significant risk devices to present more than minimal risk; thus, full IRB review for all studies involving significant risk devices is necessary.

In considering whether a study should be approved, the IRB will use the same criteria it would use in considering approval of any research involving a FDA regulated product. In considering the risks of the device as they pertain to IRB approval (as opposed to whether or not the FDA should approve the IDE), the IRB will not simply judge the increase in risk over standard treatment, but rather the risk of the procedure as a whole. The risks and benefits of a medical device compared to the risks and benefits of alternative devices or procedures will be considered by the IRB in deciding the approvability of a study involving a medical device.

Clinical investigations of intracocular lenses (IOLs) differ from other medical device investigations and are subject to specific regulation (21 CFR 813).

3. Research Involving Prospective/Retrospective Studies of Confidential Records. Research involving the study of confidential records (e.g., school, university, or medical records) is exempt providing the investigator records the data in such a manner that participants cannot be identified directly or through identifiers linked to the participant.

Research involving the study of confidential records is not exempt if the investigator records the data in such a manner that participants can be identified directly or through identifiers linked to the participant. Before the research can be initiated, the investigator must obtain IRB approval and permission from the custodian of the records to review the records.

If the investigator records the data from confidential records using subject identifiers with the intention of contacting potential participants to participate in a prospective study, the following procedures for protecting the privacy and confidentiality of the participant must be followed:

1. Before the research can be initiated, the investigator must obtain IRB approval and permission to review the records from the custodian of the records.
2. Only the name of the participant, specific selection criteria (e.g., class standing, gender, or medical diagnosis), and the name of the attending physician or other appropriate individual (e.g., participant's dentist, pharmacist, nurse, lawyer, social worker, educator) can be recorded.

Only the attending physician of the participant or other appropriate individual (e.g., subject's dentist, pharmacist, nurse, lawyer, social worker, etc.) with legal/ethical access to the confidential record should contact the potential subject. The purpose of this initial contact is to obtain written permission from the potential participant to solicit informed consent or participation in the research project. If the participant chooses not to grant permission for the release of his/her name, all data concerning the potential participant obtained by the investigator must be destroyed.

Certain kinds of research (e.g., the collection/analysis of private/sensitive information) involving the study of confidential records may require informed consent from the participant before the investigator's access to the record is granted.

4. **Research Involving Deception/Incomplete Information.** North Dakota State University subscribes to the guidelines of the American Psychological Association (APA) in the use of deception in research studies. Ethical Principle 9 E, as stated in the APA brochure titled, *Ethical Principles in the Conduct of Research with Human Participants*, May 1989, is as follows: Methodological requirements of a study may make the use of concealment or deception necessary. Before conducting such a study, the investigator has a special responsibility to (i) determine whether the use of such techniques is justified by the study's prospective scientific, educational, or applied value; (ii) determine whether alternative procedures are available that do not use concealment or deception; (iii) ensure that the participants are provided with sufficient explanation as soon as possible.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. Information about risks should never be withheld for the purpose of eliciting the cooperation of participants, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

5. **Research Involving Blood Sample Collection in a Classroom Setting.** Certain courses at NDSU include instruction in procedures for drawing blood. Students enrolled in these courses may be required to practice finger-pricking techniques on each other. IRB approval is not required for the drawing of blood in a classroom setting when the purpose is to teach students certain procedures and is not for research.

6. **Research Involving Standard Research Procedures Previously Approved by the IRB.** Research projects in some disciplines (e.g., behavioral research) involve the use of standard procedures that are used in many research projects (i.e., the cold pressor test, in which participants are asked to plunge one of their hands into a bucket of ice water and leave it there for a period of time). Although these procedures are used many times, in many research projects, each research protocol is inherently different from every other protocol (unless it is a repeat of a previous project for the purpose of gathering data on more participants or to validate previously collected data). The characteristics of subjects may be different, or variables may be introduced into a project that could

result in the potential for increased risk to subjects. For these reasons, each new protocol that involves the use of procedures that have previously received IRB approval must be reviewed by the IRB in the context of the new protocol. It will be reviewed in the appropriate review category defined by federal regulations (45 CFR 46).

7. Biomedical and Behavioral Research Involving Women and Minorities. In March 1994, the National Institutes of Health (NIH) published guidelines requiring the use of women and minorities in all research conducted or funded by the NIH. The guidelines were originally published in the Monday, March 28, 1994 issue of the *Federal Register*, vol. 59, no. 59, pp. 14508-14513 and updated October 2, 2000. These guidelines are reprinted in their entirety in Appendix F. of this manual.

As stated in the guidelines: **It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of subjects or the purpose of the research...NIH-supported biomedical and behavioral research projects involving human subjects which are exempt from the human subjects regulations should still address the inclusion of women and minorities in their study design.**

The inclusion of both women and men and of minorities in research is important, both to ensure that they receive an appropriate share of the benefits of research and that they do not bear a disproportionate burden. To the extent that participation in research offers direct benefits to the participants, under representation of men, women, or minorities denies them the opportunity to benefit. Moreover, for purposes of generalizing research results, investigators must include the widest possible range of population groups.

IRBs are empowered to approve, request modification of, or disapprove research to be submitted for NIH funding, based on their review and assessment of the extent to which the analysis criteria specified in the NIH Guidelines will be met in the proposed research. Accordingly, it is NDSU policy that the NDSU IRB will comply with the above guidelines in the review of research projects to be submitted to NIH for funding. Further, it is expected that all federal agencies that fund biomedical or behavioral research to make an effort so far as is practical to include women, men, and minorities in their research designs, regardless of the anticipated funding source.

In deliberation about appropriate selection of research participants, NDSU and the NDSU IRB have the following responsibilities:

- To help ensure that investigators understand the importance of inclusion of both genders and minorities in research and clearly delineate the expectations for the design and conduct of such research. They should assist in providing investigators with written guidance and educational opportunities for clarification.
- To specify that, when scientifically appropriate, investigators cite evidence or lack of evidence if a health situation or intervention in the proposed research may affect one gender or minority group differently and describe how the proposed research addresses that evidence. Investigators should be prepared to describe the extent to which both genders and persons of various ethnic and racial backgrounds are or have been involved in similar research.
- To help create guidelines for investigators to facilitate recruitment and retention of participants to ensure representation and sufficient involvement of targeted populations. The extent to which investigators are collaborating with those at other institutions that can involve increased numbers of men or women or populations from different minority groups must be a part of the information the IRB reviews, particularly with regard to Phase III clinical trials.
- To ensure that any special vulnerabilities of participants (e.g., educational level, socioeconomic status) are accounted for and handled appropriately. The IRB should carefully



consider if reimbursements (cash or material provisions) are appropriate to the context of the proposed research, with special attention that these reimbursements do not promote coercion or undue influence to participate or remain in a study.

- To safeguard the consent process and promote open and free communication between the researcher and the participants. Investigators and IRBs must seek to understand cultural nuances and types of foreign languages inherent in the populations to be enrolled. The possibility of illiteracy of a potential research participant must also be considered and assurances given that adequate provision has been made for appropriate translations of the consent documents or the availability of translators.

- To arrange for inclusion of women and members of minority groups on the IRB, especially if the nature and volume of the research to be conducted at the institution routinely includes these populations. IRBs should also consider consulting ad hoc advisors who could help with understanding the perspectives of various groups. Also, institutions and IRBs can encourage investigators to seek out such perspectives during planning of research protocols.

- To specify that investigators of federally-funded research provide details of the proposed involvement of humans in the research, including the characteristics of the subject population, anticipated numbers, age ranges, and health statuses. The proposed research should specify the gender and racial/ethnic composition of the participant population, as well as criteria for inclusion or exclusion of any subpopulation. If ethnic, racial, and gender estimates and continuing review are not included in the background data for a protocol, the investigators must provide a clear rationale for the exclusion of this information.

## **SECTION II**

### **REQUIREMENTS FOR INFORMED CONSENT**

The U.S. Code of Federal Regulations governing research on human subjects (45 CFR 36.116) states that, “...no investigator may involve a human being as a subject in research covered by this policy 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 any 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.”

Apart from these federal requirements, the principal reason for informing participants about an experiment is that they have a moral and ethical right to know certain things about the project before they give their consent. The use of human participants is a privilege—a favor—granted to the experimenter, rather than a right. An experiment is something that is done **to** a participant as compared to medical practice, where something is done **for** a patient.

Obtaining informed consent from a prospective participant is a two-step process: 1) giving the prospective participant sufficient information about the project to enable him/her to make an “informed” decision about whether to participate; and 2) if he/she decides to participate, obtaining his/her consent in a manner that documents the information that was given and that documents that the participant’s consent was obtained. Step 1, The Information Process, is described below. Step 2, Documentation of Informed Consent, begins on page 41.

#### **STEP 1: THE INFORMATION PROCESS**

The information about a project that a prospective participant has a right to know is called “The Elements of Informed Consent.” In compliance with 45 CFR 46.116, section 46.116, the NDSU IRB requires that the following Basic Elements of Informed Consent be communicated by means of a written consent form to prospective participants. The format for developing a consent form that contains the required information begins on page 43.

In addition to the federal minimum requirements explained below, NDSU requires that certain additional information be included in consent forms. NDSU requirements are also detailed in the consent form format beginning on page 43.

A waiver of the requirements to communicate the elements of informed consent may be obtained only under the conditions described on page 42 (Waiver of the Requirement for Informed Consent).

#### **Basic Elements of Informed Consent**

Unless the requirement for informed consent is waived, the following federally-required information must be provided to each participant when seeking informed consent:

1. a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the participant’s involvement, 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 participant;
3. a description of any benefits to the participant or to others which may reasonably be expected from research;

4. a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant;
5. a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6. 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 participants' rights and (when appropriate) whom to contact in the event of a research-related injury to the participant;
8. a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

#### **Additional Elements of Informed Consent**

When appropriate, one or more of the following elements of information must also be presented to each participant:

1. a statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. anticipated circumstances under which the participant's involvement may be terminated by the investigator without regard to the participant's consent;
3. any additional costs to the participant that may result from participation in the research;
4. the consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant;
5. a statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the subject; and
6. the approximate number of participants involved in the study.

#### **Informed Consent for Minors**

When research participants will be under the age of 18, the written consent of one or both parents, in addition to the minor's assent, is required for projects that qualify for expedited or full board review, and for some exempt projects, as well. See page 47 for policies and procedures involving the use of research subjects under the age of 18.

#### **Waiver of the Requirement for Informed Consent**

There may be situations in some research projects in which it is not feasible to communicate some or all of the elements of informed consent. In such cases, a request for waiver of some or all of the elements of informed consent may be submitted to the IRB. Section 46.116 of the Code of Federal Regulations 45 CFR 46, describes circumstances in which the IRB may approve a waiver:

**(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 or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and**

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

(d) The IRB may also approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or it may waive the requirements to obtain informed consent provided the IRB determines that:

(1) the research involves no more than minimal risk to the subjects;

(2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) the research could not practicably be carried out without the waiver or alteration; and

(4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy 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 this policy 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.

## **STEP 2: DOCUMENTATION OF INFORMED CONSENT**

Step 2, Documentation of Informed Consent, applies to all research projects that qualify for expedited and full board review, and for exempt projects for which the signed consent of participants will be obtained. Instructions for exempt projects begin on page 51.

When the Elements of Informed Consent described on pages 39-40 have been communicated to the prospective participant and he or she has decided to participate, that decision must be documented by means of the participant's signature on the consent form. The Code of Federal Regulations, 45 CFR 46, section 46.117, describes the following procedures for obtaining informed consent:

(a) Except as provided in paragraph (c) of this section (see Waiver of Signed Consent, p. 11-4), 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 (see Step 1: The Informational Process, pp II-1 and II-2). This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator must give either the subject or the representative adequate opportunity to read it and ask questions before it is signed; or

(2) 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. When this method is used, there must 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 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 must be given to the subject or representative, in addition to a copy of the short form.

### **Waiver of Signed Consent**

Section 46.117 of the Code of Federal Regulations, 45 CFR 46, describes circumstances in which the IRB may approve a waiver of the requirement to obtain signed consent:

(c) The 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. In this case, 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 in which the requirement for signed consent is waived, the IRB requires the investigator to provide participants with a written statement regarding the research.

### **Storage of Informed Consent Forms**

Signed copies of informed consent forms must be maintained by the principal investigator and be stored in a secure manner. Unless otherwise specified by federal and/or state regulations, retention of the signed consent forms is for a period of at least three years beyond the termination of the study. If the investigator resigns or graduates from North Dakota State University before the end of the designated period, the informed consent forms must be maintained by the department of record unless otherwise specified.

## FORMAT FOR INFORMED CONSENT FORMS

Unless the IRB Office issues a specific waiver, the signed consent of participants is required at NDSU for all non-exempt research projects involving human participants. In addition, it may be advisable to obtain signed consent from participants in some exempt projects (see page 46). In order to increase readability and facilitate IRB review, the following format is required for consent forms for all projects in which the signed consent participants will be obtained.

The informed consent must be written in simple language that is readily understood by the least educated, least sophisticated of the participants to be utilized. It is recommended that the language consist of short, concise sentences. Terms that are commonly used by members of a profession are a part of the profession's language, and may not be understood by the ordinary "lay" participant. If there is any doubt that a term may be understood, other words should be used or a definition of the term included, (e.g., "...4cc (about a teaspoon)"). If some of the anticipated participant population does not understand English, appropriate translation should be provided.

If the consent form will be used for parents or other legal representatives who will be consenting on behalf of a minor or other legally incompetent participants, the consent form must be written in a style that reflects the fact that it is the minor or other subject who is the participant and the consenter is agreeing to allow the said participant to participate in the study.

Use of subheadings for each section is required. The format for informed consents is as follows:

### CONSENT TO PARTICIPATE IN RESEARCH PROJECT TITLE

#### **Research Study**

You are invited to participate in a research study of Describe what is to be studied being conducted by Names of investigators and their affiliation with NDSU any other institutions.

#### **Basis for Participant Selection**

Inclusion of this section is at the discretion of the principle investigator, or at the request of the IRB. You have been selected because State reasons why, e.g., participants with specific diseases, conditions, characteristics, backgrounds. When appropriate, give the approximate number of participants in the study. When appropriate, describe exclusion criteria, e.g., pregnancy, age limitations, health restrictions.

#### **Purpose of the Study**

*(Give a clear description in simple language of the overall purpose of the research that should help the participant assess the importance of the study relative to his or her individual values. When appropriate, this statement must include not only the immediate purpose of the study, but also any larger, ultimate purpose.)*

#### **Explanation of Procedures**

*(Describe the procedures to be followed. Identify any procedures that are experimental. Include where the research will be conducted, when the research will be conducted, and how much time, per session and in total, will be required of the participant. If the research involves incomplete disclosure or deception, all participants must be debriefed as soon as possible after participation. Include a statement concerning when and where the debriefing session will be held. If debriefing may be harmful to the participants, the investigator may request a waiver of the debriefing requirement.)*

### **Potential Risks and Discomforts**

*(A risk is a potential harm that a reasonable person, in what the investigator knows or should know to be the participant's position, would be likely to consider significant in deciding whether or not to participate in the research. Risks could be physical, social, psychological, legal, or economic. Give a description of any reasonably foreseeable risks or discomforts to the participant. When appropriate, include a statement that the particular treatment or procedure may involve risks to the subject [or the embryo or fetus, if the participant is or may become pregnant] which are currently unforeseeable. For any research activity involving the consumption of food or application of chemicals or other products to the skin [cosmetic research], the following statement must be included): If you are known to have a sensitivity to any food or food ingredient, or have had violent allergic reactions to drugs, chemicals, or food ingredients, you should not participate in this study.*

### **Potential Benefits**

*(A benefit is a valued or desired outcome. Benefits associated with participation in research generally can be classified as those that accrue to the subject directly, [e.g., improvement of health status], and those that accrue to society, [acquisition of knowledge]. Describe benefits to the participant or others that could reasonably result from this research. **Financial compensation or other forms of remuneration are not considered a benefit to be derived from research participation and should be included in a separate section describing compensation.**)*

### **Alternatives to Participation**

*(Describe appropriate alternative procedures or courses of treatment, if any, that may be advantageous to the participant. If the prospective participants are students who would participate in exchange for receipt of academic credit, the consent form must describe an alternate way the student can earn the academic credit if s/he chooses not to participate. The option(s) must be comparable to research participation in terms of time, effort and educational benefit. **This is not the same as "extra credit," which is compensation for participation.**)*

### **Compensation for Participation**

*(If the participant will receive compensation, describe the amount or nature of the compensation [extra grade credits, money, free medical treatment, etc.]. The nature and amount of compensation must not constitute undue inducement to participate [i.e. the compensation alone should not serve as sufficient inducement for the subject to volunteer]. If students are given extra academic credit for participation, the amount/nature of the extra credit with respect to the award of grades must not be unduly influential.)*

### **Assurance of Confidentiality**

*(Describe the extent, if any, to which confidentiality of records identifying the participant will be maintained. In addition, the following statement must be included): Data and records created by this project are the property of the University and the investigator. You may have access to information collected on or about you by making a written request to the principle investigator. This right of access extends only to information collected on or about you and not to information collected on about others participating in the project. (This statement does not clearly spell out whether copies will be provided. In most cases, the investigator and the University would probably be willing to provide copies of data collected on him/her to the participant. It leaves open the flexibility, however, in a particular circumstance to deny copies. An example of such situations might be on a sponsored research project where information developed could be considered as proprietary information or required by contract with the sponsor.)*

*(If your project involves the investigation of a drug [Phase I-IV], non-approved use of a drug or substance, or investigation of a medical device or substance that is subject to FDA regulation, you*

must add the following statement): Representatives of the United States Department of Health and Human Services or the United States Food and Drug Administration may inspect your insert “medical records” or “research records,” as etc. to assess the results of this insert “drug treatment,” “medical device therapy,” or “research,” as appropriate.

### **Statement of Injury or Special Costs**

*(If there is a possibility of special costs to the participant because of participation, describe them. If there is a possibility of a research-related injury or other reason for medical treatment, the following paragraph must be included):* In the event that this research activity results in an injury, you should contact investigator's name at the following phone number(s) \_\_\_\_\_. Treatment will be available, including first aid, emergency treatment and follow-up care as needed. Payment for any such treatment must be provided by you and your third party payor (such as health insurance, Medicare). This paragraph does not mean that you are releasing or waiving any legal right you may otherwise have against the investigator or NDSU as a result of your participation in this research activity. *(If a commercial sponsor has agreed to provide compensation in case of injury to research participants, the extent/limitations of the compensation must be stated clearly. NDSU standard compensation statements are not to be used when a commercial sponsor has agreed to prove compensation for participant injury.)*

### **Voluntary Participation & Withdrawal from the Study**

Your participation is voluntary. Your decision whether or not to participate will not affect your insert “grade,” “treatment,” or “present or future relationship with the university (or other named organization)” as appropriate. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time. *(When appropriate, include a statement that any significant new findings developed during the course of the study that may relate to the participant's willingness to continue participation will be provided to the subject. The investigator must provide both the subject and the IRB with a written statement concerning any significant finding(s) that may potentially influence a participant's decision to continue participating in the study. In this circumstance, the investigator must re-negotiate informed consent. When appropriate, describe any anticipated circumstances, [e.g., adverse reactions], non-adherence to protocol instructions, under which the participant's involvement may be terminated by the investigator without regard to the participant's consent.)*

### **Offer to Answer Questions**

You should feel free to ask questions now or at any time during the study. If you have questions about this study, you can contact Give your name and phone number, and the name and phone number of any co-investigator. If the principal investigator is a student, the name and phone number of his/her adviser must also be included. If you have questions about the rights of research participants, contact the NDSU IRB Office, (701) 231-8908.

### **Consent Statement**

You are voluntarily making a decision whether or not to participate. Your signature indicates that you have decided to participate, having read the information provided above. You will be given a copy of this consent form to keep.

_____ Signature of Participant	_____ Printed name of Participant	_____ Date
_____ Signature of Investigator	_____ Printed name of Investigator	_____ Date



## CONSENT / ASSENT PROCEDURES FOR MINORS

Research involving minors is governed by the U.S. Code of Federal Regulations 45 CFR 46:401-409. NDSU complies with these federal regulations, and may have, in some cases, supplemented them with additional requirements.

In North Dakota, anyone under the age of 18 is considered a minor. Pregnancy does not confer majority status. A minor may, however, with IRB approval, legally consent on his/her own behalf (as a mature minor) if the research involves a treatment for which minor consent is permissible under applicable law (e.g., use of contraceptives, treatment for venereal disease, or a drug abuse).

Minors are considered a vulnerable research population because their intellectual and emotional capacities are limited. Where appropriate, studies should be conducted first on animals and adult humans, then on older children prior to involving younger children.

Legally, minors cannot give consent on their own behalf. The consent of their parent(s) or a legal guardian is, therefore, required before they can participate in any non-exempt (and some exempt) research projects. Under special circumstances (e.g., research involving neglected/abused children), the IRB may approve a waiver of parental consent. If the minor is registered as a student at North Dakota State University, and the proposed investigation involves no more than minimal risk, the requirement for parental consent may be waived.

If the research involves only minimal risk activities (e.g., venipuncture, skin biopsy, EEG, EKG, urine collection, moderate exercise, standard psychological testing), consent of only one parent or legal guardian may be obtained. If, however, the research involves greater than minimal risk activities, consent of both parents must be obtained unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has the legal responsibility for the care and custody of the child.

For research subjects under the age of seven, only parental consent is required. See guidelines for development of the parental consent form on page 44. For research participants ages seven through 17, an investigator must obtain assent of the minor in addition to parental consent, unless the subject displays intellectual/emotional development below that of the average seven year old child. A **child** assent form should be used for subjects age seven through 12 (see instructions on page 49), and a **youth** assent form should be used for participants age 13 to 18 (see instructions on page 50).

In most circumstances, a minor's deliberate objection should be regarded as a veto of his or her involvement in a research project. Parents or guardians may, however, with IRB approval, override a young child's objections to interventions that hold the prospect of direct benefit to the participant.

## FORMAT FOR PARENTAL CONSENT FORMS

The parental consent form should be written in a style that indicates it is the parent or legal guardian who is consenting to allow the minor to participate in the study. The heading for this form is:

**Parental Consent Form.** Follow the standard format for consent forms described on pages 40-41 except for the concluding consent statement, which should be as follows:

*You are voluntarily making a decision whether or not to allow your child/legal ward to participate. Your signature indicates that, having read the information provided above, you have decided to permit your child/legal ward to participate. You will be given a copy of this consent form to keep.*

---

*Signature*

---

*Date*

---

*Relation to Participant*

## FORMAT FOR CHILD ASSENT FORM

If the participant is seven through 12 years of age, both a child assent form and a parental consent form are required. The child assent form must be brief and contain extremely simplistic language written at the appropriate age level. The heading for this form should be: **Child Assent Form.**

Only the following elements need to be present on the child assent form:

- 1) a statement of the purpose of the research
- 2) a description of the procedures to be applied to the minor;
- 3) a description of the potential risks and discomforts associated with the research;
- 4) a description of any direct benefits to the minor;
- 5) a statement that the minor does not have to participate if he/she does not want to;
- 6) a statement that the minor is free to withdraw at any time;
- 7) a statement that the minor should discuss whether or not to participate with his/her parents prior to signing the form;
- 8) a statement that the parents of the minor will be asked to consent on behalf of the minor;
- 9) an offer to answer all questions.

Only the minor and the investigator should sign the child assent form. The parent or legal guardian of the minor should be given a copy of the assent form. Following is an example of a simplified concluding consent statement and signature lines:

*This research project has been explained to you and you understand what is going to be done, and why. You have talked to your parents about this project and you have decided that you would like to be a part of it. You understand that your parents [or legal guardian(s)] will be given a copy of this form to keep.*

---

*Signature of Child*

---

*Date*

---

*Investigator's Signature*

---

*Date*

## FORMAT FOR YOUTH ASSENT FORM

If the participant is 13 to 18 years of age, both a youth assent form and a parental consent form are required. The youth assent form must be written at the appropriate age level and contain simplified versions of the same elements present in the standard consent form described on pages 40-41. The heading for this form is: **Youth Assent Form**.

Only the minor and the investigator should sign the youth assent form. Give the parent or legal guardian a copy of the assent form. An example of a concluding consent statement is as follows:

*This research project has been explained to you and you understand what is going to be done, and why. You have talked to your parents about this project and you have decided that you would like to be a part of it. You understand that your parents [or legal guardian(s)] will be given a copy of this form to keep.*

---

*Signature of Youth*

---

*Date*

---

*Investigator's Signature*

---

*Date*

## FORMAT FOR INFORMED CONSENT FOR EXEMPT PROJECTS

Obtaining the signed consent of participants involved in exempt research projects is generally not required, although the NDSU IRB reserves the right to require signed consent of participants for certain exempt projects. Nevertheless, it is desirable to obtain signed consent for two reasons: (1) having the documented consent (a signature) of participants in the investigator's possession is good insurance if a problem or question should arise about a participant's involvement; and (2) students who will be involved in human research in their professional careers will undoubtedly be required to obtain signed consent of participants. Learning the process with university research projects will assist them in becoming familiar with the federal regulations that they will be required to follow later in their careers. When signed consent will be obtained from participants, the standard format for consent forms beginning on page 43 should be followed, omitting those elements of informed consent that do not apply to the project.

Even when signed consent will not be obtained, research participants have a moral and ethical right to know what is to be done to them (or required of them), and the voluntary nature of their participation before they give their consent. The NDSU IRB requires that the "elements of informed consent" described on pages 39-40 be communicated in some manner to prospective participants of exempt projects. Because some of the elements required for non-exempt projects generally do not apply to exempt projects (e.g., potential risks and discomforts, statement of injury or special costs), an abbreviated version of the elements is usually appropriate.

The method of communicating the elements of informed consent will vary, depending upon a project's design. In telephone surveys, they will obviously be communicated orally. In mail surveys, they can be communicated in a cover letter. In settings in which questionnaires will be distributed to potential subjects such as in a classroom or meeting, the elements could be communicated by means of an information sheet, attached to the front of the questionnaire that the subject can tear off and keep for his/her reference after s/he completing and returning the questionnaire. In personal interviews, especially when the investigator is doing research "in the field" and selecting participants at random as they approach, it may be difficult or impractical to present the elements of informed consent in writing. They should still be presented orally, however, and a script of what will be presented should be submitted to the IRB for exempt certification.

Regardless of the method, an example of how the elements of informed consent will be communicated must accompany the "Request for Exempt Certification" form submitted to the IRB Office. For oral presentations, a copy of the script should be submitted.

### **Sample Information Sheet for Exempt Projects**

Following is an example of an information sheet that could be attached to a questionnaire. It contains the basic elements of informed consent in narrative form. Something similar could be adapted for a cover letter to a mail survey. This format is not appropriate, however, for projects in which the signed consent of participants will be obtained. See page 43 for the standard consent form format if you intend to obtain the signed consent of participants.

Dear student, farmer, consumer, or other group:

My name is \_\_\_\_\_. I am a graduate student in department or major at North Dakota State University, and I am conducting a research project to describe the purpose of project in a few sentences. Results of this study will help us learn more about how to deal with the research problem or need.

You are invited to participate in this study. Your participation is entirely voluntary, and you may withdraw from participation at any time, with no loss of benefits. *(If subjects will not receive direct benefits or compensation, such as extra credit, you may omit the words "with no loss of*

*benefits.” For mail survey cover letters, you may wish to say something like: “Your participation is voluntary; however, your assistance would be greatly appreciated in making this a meaningful survey.” If you decide to complete this survey (or participate in this project), tear off this sheet and keep it for your information.*

*It should take about \_\_\_\_\_ minutes to complete the attached questionnaire. (Give instructions about how to complete and return the survey to you if you do not have those instructions written elsewhere.) You will receive extra credit for participating in this project, at the rate of one credit point for every 15 minutes of participation (or describe any other compensation).*

*Your identity will not be revealed in the experiment results. Only group comparisons will be made and reported in summary form. (If this is not an accurate statement of the way you will maintain the confidentiality of their responses, describe your method.)*

*If you have any questions about this project, please call me at phone number, or call my adviser at give name and campus phone number. If you have questions about the rights of human participants in research, you should contact the NDSU IRB Office, (701) 231-8908.*

*Thank you for your participation in this study. If you wish to receive a copy of the research results, please give instructions for how to let you know.*

# **SECTION III**

## **REGULATORY COMPLIANCE**

### **Part A: University Compliance**

As stated in the introduction to this manual, most federal agencies have adopted a common law that requires that all universities and other organizations that receive federal funding to support research involving human participants establish procedures that will ensure compliance with the common law. Compliance with this law, described in the Code of Federal Regulations at 45 CFR 46, is monitored by the Office for Human Research Protections (OHRP), an office of the National Institutes of Health, which is an agency of the Department of Health and Human Services.

Institutions that conduct a substantial amount of federally-sponsored human subject research may apply to OHRP for an HHS-approved multiple project assurance, which covers all research conducted at that institution for as long as the approved assurance is in effect. NDSU does not conduct enough federally-sponsored human participant research to be eligible for a multiple project assurance.

## **Part B: Investigator Compliance**

### **NON-COMPLIANCE**

NDSU IRB policy includes the minimum guidelines described in 45 CFR 46 (Appendix B). In addition, NDSU IRB policy requires that ALL research involving human participants, whether funded or regulated by a federal agency or not, must comply with NDSU and federal regulations.

Persons conducting research involving human participants have an ethical, as well as professional, obligation to ensure the safety, protection, and rights of participants. It is the intent of NDSU, through the IRB and the Office of Research Administration, to assist investigators engaged in human subject research to conduct their research along ethical guidelines reflecting professional as well as community standards. In addition, the university has an obligation to ensure that ALL research involving human subjects meets the regulations established by the United States Code of Federal Regulations (CFR). It is not the intent of the university, the IRB, or the Office of Research Administration to interfere in any way with the competent, ethical, and sound research involving human participants. However, there exists an obligation and a requirement for all parties involved to ensure that the University and its personnel are in compliance with the regulations governing human participant research. It is important for us all to observe the “spirit” as well as the “letter” of these regulations, since how we conduct research involving human participants reflects on our professional, personal, and community commitments to rigorous ethical and scientific standards of conduct.

Toward these ends, investigators must be in compliance with NDSU IRB policies and procedures regarding research involving human participants. For those instances where compliance is not forthcoming, the following policy applies:

#### **Consequences of non-compliance**

All research involving human participants **MUST** have IRB review and approval before such research can be initiated. Research that is conducted without IRB approval must be terminated immediately. Investigator(s) associated with such research must file for IRB review and approval prior to restarting a research project. Investigators who continue non-approved research should note that such non-compliance will be handled through appropriate administrative procedures initiating from the Office of the Vice President for Research, Creative Activities, and Technology Transfer.

Failure to comply with IRB directives, regulations, and procedures, including annual reports, changes in protocol, consent forms, and other requests for information or compliance emanating from the Chair or Executive Director of the IRB or the Office for Research, Creative Activities, and Technology Transfer, will result in the following:

**Project termination:** Investigators and their staff and assistants are prohibited from involving human participants in that research project until formal IRB approval/re-initiation is obtained. Such approval may be sought at the next available meeting of the IRB.

**Interruption of research support:** An additional consequence of non-compliance can be the interruption of grant funds (internal or extramural origin) allocated to that research project. Such “freezing of funds” will continue until the project and its investigators are in compliance according to the regulations as determined by the IRB Chair and the Vice President for Research, Creative Activities, and Technology Transfer.

**Report to appropriate federal agencies:** In some cases, the university is required to report to the Office for Human Research Protections (OHRP) of the National Institutes of Health any termination of a project due to non-compliance with IRB regulations and directives. Further, such non-compliance is reportable to the federal agency supporting the non-compliant research project.

### **Investigator Authority**

In order to determine that all substantive and relevant changes in protocol and/or consent documents are being reported, and in order to verify compliance with IRB regulations, the IRB shall have the authority to physically inspect any research premises or review non-confidential research documents relating to the protocol and procedures being used in human participant experimentation. Generally, the investigator will be asked to provide copies of relevant and necessary documents for IRB review. Such document requests are in addition to that generated in the project progress/completion report. In most cases, this will only occur when there is an indication that a substantive change is in effect which has not been reported, or that unforeseen risks to participants are present or alleged.

Failure to comply with such an IRB request for information may result in suspension or termination of IRB approval of research.

### **Authority to Suspend or Terminate IRB Approval of Research**

According to **45 CFR 46.113**:

**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 to the investigator, appropriate institutional officials, and the Secretary (of Health and Human Services, via OHRP).**

### **Appeal Procedures**

There are no formal appeal procedures associated with IRB review. The IRB is not judicial body, but a review board embodied to consider and uphold the rights, welfare, and protection of human participants in research. IRB approval for research that has been suspended or terminated can be reinstated with a demonstration that the protocol/project complies with IRB and federal policies. Similarly, a disapproved project need only be altered such that it can secure approval. An appeal process assumes that the decision of an IRB can be overturned by another group. An IRB ruling is not subject to appeal nor can it be overturned by another group. Only the IRB can alter its previous determination.

### **Enactment**

These procedures and policies are considered to be in effect immediately upon approval by authorized university officials and remain in effect and enforceable until otherwise amended or repealed. IRB policies and guidelines are in effect for all university personnel from the moment personnel become officially affiliated with NDSU (contractual start date) until they are no longer officially affiliated with NDSU in any capacity. Policies, procedures, and guidelines are subject to change through revisions in relevant Federal law, NDSU IRB rulings, and directives from OHRP.

It is likely that not all possible contingencies have been foreseen or considered in these guidelines and procedures. The IRB, a committee of representatives from each college along with non-university members, strives to deliver the best possible service regarding the review of research involving human subjects. To assist in the long-term goal of establishing the means and the willingness to assure adequate protection of human subjects, the IRB needs the cooperation of the research community of scholars at NDSU.

It is the intent of the IRB to invite input from investigators and interested parties regarding revisions and updates to these guidelines and procedures. Where possible and appropriate, such recommendations will be incorporated into IRB policies and procedures. Working together, we can develop a streamlined, but effective system of review and assurance creating an ethical and professional environment for human participants in research.



## **APPENDICES**

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45 CFR 46: Protection of Human Subjects	Appendix B
Deviations from 45 CFR 46 by Certain Federal Agencies	Appendix C
21 CFR 50 Food & Drug Administration Guidelines for the Protection of Human Subjects	Appendix D
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NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research	Appendix F
FDA Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs	Appendix G

# **ORIGINAL SCHEDULE OF APPOINTMENT TO IRB** (October 13, 1986)

In order to have membership renewal or replacement of board members on a “staggered” basis, the following appointment scheme will be employed. Year indicated is the year in which that position is first up for renewal, unless the position becomes vacant (through resignation or departure from university service) beforehand:

Agricultural Experiment Station	1988
College of Agriculture	1988
College of Engineering & Architecture	1988
College of Science & Mathematics	1988
College of Humanities & Social Sciences	1987
College of Pharmacy	1987
*College of Home Economics	1987
*School of Education	1987
College of Business Administration	1987
**NDSU Extension Service	1989
Physician member	1989
Non-NDSU member	1989
Attorney member	permanent non-voting
IRB Executive Director	permanent non-voting
Vice President for Research, Creative Activities and Technology Transfer	ex-officio (non-voting)

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\*College of Home Economics, School of Education, and Department of Health, Physical Education and Recreation were combined in 1992 to form the College of Human Development and Education (HDE).

\*\*Representation from the NDSU Extension Service has been discontinued. Their primary mission is education and service and they do very little research in the sense of scholarly activity.

**Appendix B: 45 CFR 46**

CODE OF FEDERAL REGULATIONS

TITLE 45  
PUBLIC WELFARE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

OFFICE OF HUMAN RESEARCH PROTECTIONS

**PART 46 – PROTECTION OF HUMAN SUBJECTS**

Subpart A – Basic Policy for Protection of Human Research Subjects  
(effective as of August 19, 1991, revised October 1, 2000)

Subpart B – Additional Protections Pertaining to Research, Development,  
and Related Activities Involving Fetuses, Pregnant Women,  
and Human In Vitro Fertilization  
(revised October 1, 2000)

Subpart C – Additional Protections Pertaining to Biomedical and  
Behavioral Research Involving Prisoners as Subjects  
(revised October 1, 2000)

Subpart D – Additional Protections for Children Involved as Subjects in  
Research  
(revised October 1, 2000)

**4 CFR45 CFR 46: Protection of Human Subjects 46: Protection of Human Subjects**  
45 CFR 46: Protection of Human Subjects

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## Subpart A – Basic HHS Policy for Protection of Human Research Subjects

Source: 56 FR 28012, June 18, 1991

### **SECTIONS**

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111	Criteria for IRB approval of research for certain kinds of research involving no more than minimal risk and for minor changes in approved research.
112	Review by institution.
113	Suspension or termination of IRB approval of research.
114	Cooperative research.
115	IRB records.
116	General requirements for informed consent.
117	Documentation of informed consent.
118	Applications and proposals lacking definite plans for involvement of human subjects.
119	Research undertaken without the intention of involving human subjects.
120	Evaluation and disposition of applications and proposals for research to be conducted or supported by a federal Department or Agency.
121	[Reserved]
122	Use of Federal funds.
123	Early termination of research support: Evaluation of Applications and proposals.
124	Conditions.

The following federal agencies have accepted the basic HHS policy for protection of human research subjects (45 CFR 46, Subpart A, Sections 101--124 [Code of Federal Regulations]). Following each federal agency is the location in the Code of Federal Regulations where this Subpart is described:

Department of Agriculture	7 CFR Part 1c, Sections 1c.101 – 1c.124
Department of Energy	10 CFR Part 745, Sections 745.101 – 745.124
NASA	14 CFR Part 1230, Sections 1230.101 – 1230.124
Department of Commerce	15 CFR Part 27, Sections 27.101 – 27.124
Consumer Product Safety Commission	16 CFR Part 1028, Sections 1028.101 – 1028.124
International Development Cooperation Agency,	
Agency for International Development	22 CFR Part 225, Sections 225.101 – 225.124
Department of Housing & Urban Development	24 CFR Part 60, Sections 60.101 – 60.124
Department of Justice	28 CFR Part 46, Sections 46.101 – 46.124
Department of Defense	32 CFR Part 219, Sections 219.101 – 219.124
Department of Education	34 CFR Part 97, Sections 97.101 – 97.124
Department of Veterans Affairs	38 CFR Part 16, Sections 16.101 – 16.124
Environmental Protection Agency	40 CFR Part 26, Sections 26.101 – 26.124
Department of Health and Human Services	45 CFR Part 46, Sections 46.101 – 46.124
National Science Foundation	45 CFR Part 690, Sections 690.101 – 690.124
Department of Transportation	49 CFR Part 11, Sections 11.101 – 11.124

## **Subpart A – Basic HHS Policy for Protection of Human Research Subjects**

### **SECTION 46.101 TO WHAT DOES THIS POLICY APPLY?**

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in Section 46.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in Section 46.102(e) must be reviewed and approved, in compliance with Section 46.101, Section 46.102, and Section 46.107 through Section 46.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(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), survey procedures, interview procedures, or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) 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.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below

the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. (An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.) In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, Department of Health and Human Services (HHS), and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures<sup>1</sup>.

## **SECTION 46.102 DEFINITIONS**

(a) Department or agency head means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

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

(c) 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.

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

(e) Research subject to regulation, and similar terms, are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity (for example, Investigational New Drug requirements administered by the Food and Drug



Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(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 associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) IRB means an Institutional Review Board established in accord with and for the purposes expressed in this policy.

(h) IRB approval means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) Certification means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

#### **SECTION 46.103 ASSURING COMPLIANCE WITH THIS POLICY—RESEARCH CONDUCTED OR SUPPORTED BY ANY FEDERAL DEPARTMENT OR AGENCY**

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, HHS, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Protection from Research Risks, HHS.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head 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. Assurances applicable to federally supported or conducted research shall at a minimum include:

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<sup>1</sup> Institutions with HHS-approved assurances on file will abide by provisions of title 45 CFR part 46 subparts A-D. Some of the other departments and agencies have incorporated all provisions of title 45 CFR 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, subparts B and C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

(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 whether the research is subject to federal regulation. 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 this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under Section 46.101 (b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, 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 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 department or agency head, unless in accordance with Section 46.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, HHS.(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; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such 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 when necessary to eliminate apparent immediate hazards to the subject.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and action 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; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such 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 when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

(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 this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head'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 department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head 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) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under Section 46.101(b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by Section 46.103 of this policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by Section 46.103 of the policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

**SECTION 46.104 [Reserved]**

**SECTION 46.105 [Reserved]**

**SECTION 46.106 [Reserved]**

**SECTION 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, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. 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, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(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 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.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

**SECTION 46.108 IRB FUNCTIONS AND OPERATIONS**

In order to fulfill the requirements of this policy, each IRB shall:

(a) Follow written procedures in the same detail as described in Section 46.103(b)(4) and, to the extent required, by Section 46.103(b)(5).

(b) Except when an expedited review procedure is used (see Section 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.

#### **SECTION 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 this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with Section 46.116. The IRB may require that information, in addition to that specifically mentioned in Section 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 Section 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 this policy 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.

#### **SECTION 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, HHS, has established, and published as a Notice 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 after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REGISTER. A copy of the list is available from the Office for Human Research Protections, Division of Policy & Assurance, 6100 Executive Boulevard, Rockville, Maryland 20892-7507.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

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 Section 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 department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

## **SECTION 46.111 CRITERIA FOR IRB APPROVAL OF RESEARCH**

(a) In order to approve research covered by this policy 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 and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(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 Section 46.116.

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

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

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

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

## **SECTION 46.112 REVIEW BY INSTITUTION**

Research covered by this policy 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.

## **SECTION 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 department or agency head.

## **SECTION 46.114 COOPERATIVE RESEARCH**

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

#### **SECTION 46.115 IRB RECORDS**

(a) An institution, or when 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 in the same detail as described in Section 46.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in Section 46.103(b)(4) and Section 46.103(b)(5).

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

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

#### **SECTION 46.116 GENERAL REQUIREMENTS FOR INFORMED CONSENT**

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy 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) or (d) 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;
  - (6) 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 or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; 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 in this section, 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 this policy 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 this policy 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.

#### **SECTION 46.117 DOCUMENTATION OF INFORMED CONSENT**

(a) Except as provided in paragraph (c) 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 Section 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 Section 46.116 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 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 in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

#### **SECTION 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 departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility;



research training grants in which 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 exempted or waived under Section 46.101(b) or (i), 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 this policy, and certification submitted, by the institution, to the department or agency.

#### **SECTION 46.119 RESEARCH UNDERTAKEN WITHOUT THE INTENTION OF INVOLVING HUMAN SUBJECTS**

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

#### **SECTION 46.120 EVALUATION AND DISPOSITION OF APPLICATIONS AND PROPOSALS FOR RESEARCH TO BE CONDUCTED OR SUPPORTED BY A FEDERAL DEPARTMENT OR AGENCY**

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head 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 research to the subjects and others, and the importance of the knowledge gained or to be gained.

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

#### **SECTION 46.121 [Reserved]**

#### **SECTION 46.122 USE OF FEDERAL FUNDS**

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

#### **SECTION 46.123 EARLY TERMINATION OF RESEARCH SUPPORT; EVALUATION OF APPLICATIONS AND PROPOSALS**

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy, the department or agency head 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 or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgement of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

#### **SECTION 46.124 CONDITIONS**

With respect to any research project or any class of research projects, the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

## **45 CFR 46 Subpart B – Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization**

Source: Federal Register—59FR 28276 June 1, 1994.

### **SECTIONS:**

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This Subpart B describes regulations required by the various agencies, departments and institutes of the Department of Health and Human Services. For requirements of other federal agencies for these activities, see the appropriate agency's Code of Federal Regulations.

## **45 CFR 46 Subpart B – Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization**

### **SECTION 46.201 APPLICABILITY**

- (a) The regulations in this subpart are applicable to all Department of Health and Human Services grants and contracts supporting research, development, and related activities involving: (1) The fetus; (2) pregnant women, and (3) human in vitro fertilization.
- (b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.
- (c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

### **46.202 PURPOSE**

It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

### **SECTION 46.203 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) Pregnancy encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.
- (c) Fetus means the product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable.
- (d) Viable as it pertains to the fetus means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a fetus is viable for purposes of this subpart. If a fetus is viable after delivery, it is a premature infant.
- (e) Nonviable fetus means a fetus ex utero which, although living, is not viable.
- (f) Dead fetus means a fetus ex utero which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).
- (g) In vitro fertilization means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

### **SECTION 46.204 ETHICAL ADVISORY BOARDS**

- (a) One or more Ethical Advisory Boards shall be established by the Secretary. Members of these board(s) shall be so selected that the board(s) will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research scientists, physicians, psychologists, sociologists, educators, lawyers, and ethicists, as well as representatives of the general public. No board member may be a regular, full-time employee of the Department of Health and Human Services.

(b) At the request of the Secretary, the Ethical Advisory Board shall render advice consistent with the policies and requirements of this part as to ethical issues, involving activities covered by this subpart, raised by individual applications or proposals. In addition, upon request by the Secretary, the Board shall render advice as to classes of applications or proposals and general policies, guidelines, and procedures.

(c) A Board may establish, with the approval of the Secretary, classes of applications or proposals which:

- (1) Must be submitted to the Board, or
- (2) need not be submitted to the Board.

Where the Board so establishes a class of applications or proposals which must be submitted, no application or proposal within the class may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

#### **SECTION 46.205 ADDITIONAL DUTIES OF INSTITUTIONAL REVIEW BOARDS IN CONNECTION WITH ACTIVITIES INVOLVING FETUSES, PREGNANT WOMEN, OR HUMAN IN VITRO FERTILIZATION**

(a) In addition to the responsibilities prescribed for Institutional Review Boards under Subpart A of this part, the applicant's or offeror's Board shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) Determine that all aspects of the activity meet the requirements of this subpart;

(2) Determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made by the applicant or offeror for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the Institutional Review Board or subject advocates in: (i) overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen);

(3) Carry out such other responsibilities as may be assigned by the Secretary.

(b) No award may be issued until the applicant or offeror has certified to the Secretary that the Institutional Review Board has made the determinations required under paragraph (a) of this section and the Secretary has approved these determinations, as provided in Section 46.120 of Subpart A of this part.

(c) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been established under Subpart A of this part.

#### **SECTION 46.206 GENERAL LIMITATIONS**

(a) No activity to which this subpart is applicable may be undertaken unless:

(1) Appropriate studies on animals and nonpregnant individuals have been completed;

(2) Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.

(3) Individuals engaged in the activity will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and

(4) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

(b) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

#### **SECTION 46.207 ACTIVITIES DIRECTED TOWARD PREGNANT WOMEN AS SUBJECTS**

(a) No pregnant woman may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if: (1) The purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

#### **SECTION 46.208 ACTIVITIES DIRECTED TOWARD FETUSES IN UTERO AS SUBJECTS**

(a) No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless: (1) the purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained; (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

#### **SECTION 46.209 ACTIVITIES DIRECTED TOWARD FETUSES EX UTERO, INCLUDING NON-VIABLE FETUSES, AS SUBJECTS**

(a) Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity covered by this subpart unless:

(1) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

(2) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

(b) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:

(1) Vital functions of the fetus will not be artificially maintained;

(2) Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(c) In the event the fetus ex utero is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

(d) An activity permitted under paragraph (a) or (b) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained; (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

#### **SECTION 46.210 ACTIVITIES INVOLVING THE DEAD FETUS, FETAL MATERIAL, OR THE PLACENTA**

Activities involving the dead fetus, mascerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

#### **SECTION 46.211 MODIFICATION OR WAIVER OF SPECIFIC REQUIREMENTS**

Upon the request of an applicant or offeror (with the approval of its Institutional Review Board), the Secretary may modify or waive specific requirements of this subpart, with the approval of the Ethical Advisory Board after such opportunity for public comment as the Ethical Advisory Board considers appropriate in the particular instance. In making such decisions, the Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modification or waiver and that such benefits cannot be gained except through a modification or waiver. Any such modifications or waivers will be published as notices in the FEDERAL REGISTER.

## **45 CFR 46 Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects**

Source: 43 FR 53655, Nov. 16, 1978

### **SECTIONS:**

45 CFR 46.301	Applicability.
302	Purpose.
303	Definitions.
304	Composition of Institutional Review Boards where prisoners are involved.
305	Additional duties of the Institutional Review Boards where prisoners are involved.
304	Permitted research involving prisoners.

This Subpart C describes regulations required by the various agencies, departments and institutes of the Department of Health and Human Services. For requirements of other federal agencies for these research activities, see the appropriate agency's Code of Federal Regulations.

## **45 CFR 46 Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects**

### **SECTION 46.301 APPLICABILITY**

- (a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.
- (b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.
- (c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

### **SECTION 46.302 PURPOSE**

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

### **SECTION 46.303 DEFINITIONS**

As used in this subpart:

- (a) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.
- (b) DHHS means the Department of Health and Human Services.
- (c) Prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.
- (c) Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

### **SECTION 46.304 COMPOSITION OF INSTITUTIONAL REVIEW BOARDS WHERE PRISONERS ARE INVOLVED**

In addition to satisfying the requirements in Section 46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

- (a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
- (b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.



## **SECTION 46.305 ADDITIONAL DUTIES OF INSTITUTIONAL REVIEW BOARDS WHERE PRISONERS ARE INVOLVED**

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

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

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

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

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

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

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

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

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

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

## **SECTION 46.306 PERMITTED RESEARCH INVOLVING PRISONERS**

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

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

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

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

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

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

(iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research.

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

## **45 CFR 46 Subpart D – Additional Protections for Children Involved as Subjects in Research**

Source: 56 FR 28032, June 18, 1991

### **SECTIONS:**

45 CFR 46.401	To what do these regulations apply?
402	Definitions.
403	IRB duties.
404	Research not involving greater than minimal risk.
405	Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
406	Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
407	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
408	Requirements for permission by parents or guardians and for assent by children.
409	Wards.

This Subpart D describes regulations required by the various agencies, departments and institutes of the Department of Health and Human Services. For requirements of other federal agencies for these research activities, see the appropriate agency's Code of Federal Regulations.

## **45 CFR 46 Subpart D – Additional Protections for Children Involved as Subjects in Research**

### **SECTION 46.401 TO WHAT DO THESE REGULATIONS APPLY?**

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

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

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of Section 46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at 46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at 46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of 46.101 of Subpart A are applicable to this subpart.

### **SECTION 46.402 DEFINITIONS**

The definitions in 46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

(b) Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) Parent means a child's biological or adoptive parent.

(e) Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

### **SECTION 46.403 IRB DUTIES**

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

### **SECTION 46.404 RESEARCH NOT INVOLVING GREATER THAN MINIMAL RISK**

DHHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in Section 46.408.

**SECTION 46.405 RESEARCH INVOLVING GREATER THAN MINIMAL RISK BUT PRESENTING THE PROSPECT OF DIRECT BENEFIT TO THE INDIVIDUAL SUBJECT**

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

- (a) The risk is justified by the anticipated benefit to the subjects;
- (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in Section 46.408.

**SECTION 46.406 RESEARCH INVOLVING GREATER THAN MINIMAL RISK, AND NO PROSPECT OF DIRECT BENEFIT TO THE INDIVIDUAL SUBJECTS, BUT LIKELY TO YIELD GENERALIZABLE KNOWLEDGE ABOUT THE SUBJECT'S DISORDER OR CONDITION**

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

- (a) The risk represents a minor increase over minimal risk;
- (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- (d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in Section 46.408.

**SECTION 46.407 RESEARCH NOT OTHERWISE APPROVABLE WHICH PRESENTS AN OPPORTUNITY TO UNDERSTAND, PREVENT, OR ALLEVIATE A SERIOUS PROBLEM AFFECTING THE HEALTH OR WELFARE OF CHILDREN**

DHHS will conduct or fund research in which the IRB does not believe meets the requirements of Sections 46.404, 46.405, or 46.406 only if:

- (a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children; and
- (b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
  - (1) That the research in fact satisfies the conditions of Sections 46.404, 46.405, 46.406, as applicable, or
  - (2) The following:
    - (i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The research will be conducted in accordance with sound ethical principles;

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in Section 46.408.

#### **SECTION 46.408 REQUIREMENTS FOR PERMISSION BY PARENTS OR GUARDIANS AND FOR ASSENT BY CHILDREN**

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgement may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with Section 46.116 of Subpart A.

(b) In addition to the determinations required under other applicable section of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by Section 46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under Section 46.404 or 46.405. Where research is covered by Sections 46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonable available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in Section 46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by Section 46.117 of Subpart A.

(c) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

#### **SECTION 46.409 WARDS**

(a) Children who are wards of the State or any other agency, institution, or entity can be included in research approved under Section 46.406 or 46.407 only if such research is:

(1) Related to their status as a ward; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

## **Appendix C: Deviations from 45 CFR 46 by Certain Federal Agencies**

### **1. FOOD AND DRUG ADMINISTRATION, Parts 50 and 56**

Source: 53 FR 45678, November 10, 1988; 56 FR 28025, June 18, 1991

FDA concurs with the final Model Policy. However, FDA must diverge from 45 CFR 46.101(h) of the final Model Policy with regard to those clinical investigations that take place in a foreign country and are conducted under a research permit granted by FDA. Such investigations must be carried out in accordance with the act, which establishes certain requirements for the conduct of such investigations (see, e.g., 21 U.S.C. 355(i), 357(d)(3), and 360j(g)). For these investigations, FDA does not have the authority to accept the procedures followed in a foreign country in lieu of the procedures required by the act. FDA must also depart from 45 CFR 46.116(d) of the final Model Policy (see 21 CFR 50.20). The act requires that informed consent be obtained from all subjects of clinical investigations except in very limited circumstances (see, e.g., 21 U.S.C. 355(i), 357(d)(3), and 360j(g)(3)(D), which establish requirements for the conduct of clinical investigations for drugs, antibiotic drugs, and medical devices, respectively). FDA does not have the authority under the act to waive this requirement.

### **2. DEPARTMENT OF EDUCATION, 34 CFR Part 350: Disability and Rehabilitation Research: General Provisions; Part 356: Disability and Rehabilitation Research: Research Fellowships**

Source: 56 FR 28029, June 18, 1991

Sections 350.3(d) and 356.3(c) are amended by revising those respective paragraphs to read as follows:

(2) Each Institutional Review Board (IRB) established under part 97 must have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB must be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB must 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 must therefore include persons knowledgeable in these areas. *\*When an IRB reviews research that purposefully requires inclusion of handicapped children or mentally disabled persons as research subjects, the IRB must include at least one person primarily concerned with the welfare of these research subjects.* If an IRB regularly reviews another vulnerable category of subjects, such as non-handicapped children, prisoners, pregnant women, or handicapped adults, consideration must also be given to the inclusion of one or more individuals who are knowledgeable about the experience in working with these subjects.

*\*deviation from 45 CFR 46*

## **Appendix D: 21 CFR 50**

### CODE OF FEDERAL REGULATIONS

#### TITLE 21 FOOD AND DRUGS

#### DEPARTMENT OF HEALTH AND HUMAN SERVICES

#### FOOD AND DRUG ADMINISTRATION

### **PART 50 – PROTECTION OF HUMAN SUBJECTS**

Subpart A – General Provisions  
(revised April 1, 2000)

Subpart B – Informed Consent of Human Subjects  
(revised April 1, 2000)

Subpart C – Protections Pertaining to Clinical Investigations Involving  
Prisoners as Subjects  
(revised April 1, 1998)



## **21 CFR 50: Protection of Human Subjects**

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## **21 CFR 50 Subpart A—General Provisions**

### **SECTION 50.1 SCOPE**

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 406, 409, 502, 503, 505, 510, 513-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of title 21, unless otherwise noted.

### **SECTION 50.3 DEFINITIONS**

As used in this part:

(a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201--902, 52 Stat. 1040 et seq. as amended (21 U.S.C. 321--392)).

(b) Application for research or marketing permit includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in Secs. 170.30 and 570.30.

(4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in Sec. 180.1.

(5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) Data and information about an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for these drugs, described in Sec. 314.300 of this chapter.

(12) An application for a biologics license, described in part 601 of this chapter.

(13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809.

(15) An Application for an Investigational Device Exemption, described in part 812.

(16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.

(17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.

(18) An application for premarket approval of a medical device, described in section 515.

(19) A product development protocol for a medical device, described in section 515.

(20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.

(21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in Sec. 1010.4.

(22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in Sec. 1010.5.

(c) Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

(d) Investigator means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e) Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(f) Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

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

(h) Institution means any public or private entity or agency (including Federal, State, and other agencies). The word facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.

(i) Institutional review board (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

(j) Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

(k) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(l) 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.

(m) Family member means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

## **21 CFR 50 SUBPART B—Informed Consent of Human Subjects**

### **SECTION 50.20 GENERAL REQUIREMENTS FOR INFORMED CONSENT**

Except as provided in Secs. 50.23 and 50.24, no investigator may involve a human being as 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.

### **SECTION 50.23 EXCEPTION FROM GENERAL REQUIREMENTS**

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

(d)

(1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements of section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved the Secretary of Defense must first request such a determination from the President, and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met.

(i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND.

(ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness.

(iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug.

(iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission.

(v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by Sec. 56.115(a)(2) of this chapter.

(vi) DOD has explained:

(A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional;

(B) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and

(C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

(vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient.

(viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10

U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.

(ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section.

(x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter.

(xi) DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

(xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence.

(xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request.

(xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use.

(xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria.

(xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent.

(xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in the Federal Register describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

(xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law.

(2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain

any necessary security clearances. This IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by Sec. 56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review.

(3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve:

(i) The required information sheet;

(ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written);

(iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and

(iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved.

(4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

(5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations.

#### **SECTION 50.24 EXCEPTION FROM INFORMED CONSENT FOR EMERGENCY RESEARCH**

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's



condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with Sec. 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under Secs. 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

## **SECTION 50.25 ELEMENTS OF INFORMED CONSENT**

(a) Basic elements of informed consent. 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 and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) 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.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that 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.

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

(c) 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 for informed consent to be legally effective.

(d) 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.

#### **SECTION 50.27 DOCUMENTATION OF INFORMED CONSENT**

(a) Except as provided in Sec. 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

(b) Except as provided in Sec. 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by Sec. 50.25. 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.

(2) A short form written consent document stating that the elements of informed consent required by Sec. 50.25 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 the 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.

### **Subpart C—Protection Pertaining to Clinical Investigations Involving Prisoners as Subjects (April 1, 1998 version)**

#### **SECTION 50.40 APPLICABILITY**

(a) The regulations in this subpart apply to all clinical investigations involving prisoners as subjects that are regulated by the Food and Drug Administration under sections 505(i), 507(d), and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations involving prisoners that support application for research or marketing permits for products regulated by the Food and Drug Administration.

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

#### **SECTION 50.42 PURPOSE**

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

#### **SECTION 50.44 RESTRICTIONS ON CLINICAL INVESTIGATIONS INVOLVING PRISONERS**

(a) Except as provided in Sec. 50.44(b), clinical investigations regulated by the Food and Drug Administration under sections 505(i), 507(d), and 505(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration may not involve prisoners as subjects.

(b) Clinical investigations that are regulated by the Food and Drug Administration under sections 505(i), 507(d), or 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, may involve prisoners as subjects only if the institution responsible for the conduct of the clinical investigation has certified to the Food and Drug Administration that the institutional review board has approved the clinical investigation under Sec. 50348; and

(1) (i) In the judgment of the Food and Drug Administration, the proposed clinical investigation involves solely research on practices both innovative and accepted, which have the intent and reasonable probability of improving the health and well-being of the subjects; and

(ii) In cases in which these studies require the assignment of prisoners in a manner consistent with protocols approved by the institutional review boards to control groups that may not benefit from the research, the study may proceed only after the Food and Drug Administration has consulted with appropriate experts, including experts in penology, medicine, and ethics, and has published notice in the Federal Register of its intent to approve such research; or

(2) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis, which is much more prevalent in prisons than elsewhere) provided that the Food and Drug Administration has consulted with appropriate experts, including experts in penology, medicine, and ethics, and has published notice in the Federal Register of its intent to approve such research; subject to approval of the Food and Drug Administration, prisoners may participate in the research even though they are assigned, in a manner consistent with protocols approved by the institutional review board, to control groups that may not benefit from the research.

#### **SECTION 50.46 COMPOSITION OF INSTITUTIONAL REVIEW BOARDS WHERE PRISONERS ARE INVOLVED**

In addition to satisfying any other requirements of governing institutional review boards set forth in this chapter, an institutional review board, in carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the institutional review board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the institutional review board.

(b) At least one member of the institutional review board shall be a prisoner, or a prisoner advocate with appropriate background and experience to serve in that capacity, except that if a particular research project is reviewed by more than one institutional review board, only one institutional review board need satisfy this requirement.

## **SECTION 50.48 ADDITIONAL DUTIES OF THE INSTITUTIONAL REVIEW BOARDS WHERE PRISONERS ARE INVOLVED**

(a) In addition to all other responsibilities prescribed for institutional review boards under this chapter, the institutional review board shall review clinical investigations covered by this subpart and approve such clinical investigation only if it finds that:

(b)

(1) The research under review represents one of the categories of research permitted under Sec. 50.44(b) (1) and (2);

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

(3) The risks involved in the clinical investigation are commensurate with risks that would be accepted by non-prisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoner; unless the principal investigator provides to the institutional review board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that research project;

(5) Any information given to subjects is presented in language which is appropriate for the subject population

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

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

(b) The institutional review board shall carry out such other duties as may be assigned by the Food and Drug Administration.

(c) The institution shall certify to the Food and Drug Administration, in such form and manner as the Food and Drug Administration may require, that the duties of the institutional review board under this section have been fulfilled.

## **Appendix E: 21 CFR 56**

CODE OF FEDERAL REGULATIONS

TITLE 21  
FOOD AND DRUGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

### **PART 56 – INSTITUTIONAL REVIEW BOARDS**

Subpart A – General Provisions  
(revised April 1, 2000)

Subpart B – Organization and Personnel  
(revised April 1, 2000)

Subpart C – IRB Functions and Operations  
(revised April 1, 2000)

Subpart D – Records and Reports  
(revised April 1, 2000)

Subpart E – Administrative Action for Noncompliance  
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## **21 CFR 56 Subpart A—General Provisions**

### **SECTION 56.101 SCOPE**

(a) This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

### **SECTION 56.102 DEFINITIONS**

As used in this part:

(a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-392)).

(b) Application for research or marketing permit includes:

(1) A color additive petition, described in part 71.

(2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in Sec. 170.35.

(3) A food additive petition, described in part 171.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in Sec. 180.1.

(5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information regarding an over-the-counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) An application for a biological product license, described in part 601.

(11) An application for a biologics license, described in part 601 of this chapter.

(12) An Application for an Investigational Device Exemption, described in parts 812 and 813.

(13) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in part 860.

(14) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in part 861.

(15) An application for premarket approval of a medical device for human use, described in section 515 of the act.

(16) A product development protocol for a medical device for human use, described in section 515 of the act.

(17) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act.

(18) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in Sec. 1010.4.

(19) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in Sec. 1010.5.

(20) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003.

(c) Clinical investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.

(d) Emergency use means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

(e) Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

(f) Institution means any public or private entity or agency (including Federal, State, and other agencies). The term facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.

(g) Institutional Review Board (IRB) means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

(h) Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.



(i) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) Sponsor means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(k) Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.

(l) Test article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

(m) IRB approval means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

#### **SECTION 56.103 CIRCUMSTANCES IN WHICH IRB REVIEW IS REQUIRED**

(a) Except as provided in Secs. 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

(b) Except as provided in Secs. 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

#### **SECTION 56.104 EXEMPTIONS FROM IRB REQUIREMENT**

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

#### **SECTION 56.105 WAIVER OF IRB REQUIREMENT**

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

### **Subpart B—Organization and Personnel**

#### **SECTION 56.107 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, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the 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 or 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, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.

(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 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.

(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.

### **Subpart C—IRB Functions and Operations**

#### **SECTION 56.108 IRB FUNCTIONS AND OPERATIONS**

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

(a) Follow written procedures:

(1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;

(2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review;

(3) for ensuring prompt reporting to the IRB of changes in research activity; and

(4) for ensuring 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 human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of:

(1) Any unanticipated problems involving risks to human subjects or others;

(2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or

(3) any suspension or termination of IRB approval.

(c) Except when an expedited review procedure is used (see Sec. 56.110), 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.

## **SECTION 56.109 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 Sec. 50.25. The IRB may require that information, in addition to that specifically mentioned in Sec. 50.25, 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 in accordance with Sec. 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds 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; or

(2) The IRB may, for some or all subjects, find that the requirements in Sec. 50.24 of this chapter for an exception from informed consent for emergency research are met.

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(e) 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. For investigations involving an exception to informed consent under Sec. 50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under Sec. 50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.

(f) 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.

(g) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under Sec. 50.24 of this chapter a copy of information that has been publicly disclosed under Sec. 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter. The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.

#### **SECTION 56.110 EXPEDITED REVIEW PROCEDURES FOR CERTAIN KINS OF RESEARCH INVOLVING NO MORE THAN MINIMAL RISK, AND FOR MINOR CHANGES IN APPROVED RESEARCH**

(a) The Food and Drug Administration 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 use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) 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 IRB chairperson from among the 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 nonexpedited review procedure set forth in Sec. 56.108(c).

(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 Food and Drug Administration 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.

#### **SECTION 56.111 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 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 that 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 and should be

particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

(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 part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by Sec. 50.27.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure 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) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

#### **SECTION 56.112 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.

#### **SECTION 56.113 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 Food and Drug Administration.

#### **SECTION 56.114 COOPERATIVE RESEARCH**

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

### **Subpart D – Records and Reports**

#### **SECTION 56.115 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 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, a member of governing panel or board, stockholder, paid or unpaid consultant.

(6) Written procedures for the IRB as required by Sec. 56.108 (a) and (b).

(7) Statements of significant new findings provided to subjects, as required by Sec. 50.25.

(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 Food and Drug Administration at reasonable times and in a reasonable manner.

(c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

## **Subpart E – Administrative Actions for Noncompliance**

### **SECTION 56.120 LESSER ADMINISTRATIVE ACTIONS**

(a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.

(b) On the basis of the IRB's or the institution's response, FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the agency may:

(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;

(2) Direct that no new subjects be added to ongoing studies subject to this part;

(3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or

(4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.

(c) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

## **SECTION 56.121 DISQUALIFICATION OF AN IRB OR INSTITUTION**

(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under Sec. 56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in part 16.

(b) The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:

(1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and

(2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

(c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in the Federal Register.

(d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in Sec. 56.123.

## **SECTION 56.122 PUBLIC DISCLOSURE OF INFORMATION REGARDING REVOCATION**

A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under part 20.

## **SECTION 56.123 REINSTATEMENT OF AN IRB OR AN INSTITUTION**

An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under Sec. 56.121(c).

## **SECTION 56.124 ACTION ALTERNATIVE OR ADDITIONAL TO DISQUALIFICATION**

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.

**Appendix F: NIH Guidelines on the Inclusion of Women and Minorities as  
Subjects in Clinical Research**

IMPLEMENTED IN ACCORDANCE WITH SECTION 492B  
OF THE PUBLIC HEALTH SERVICE ACT,  
ADDED BY THE NIH REVITALIZATION ACT OF 1993,  
PUBLIC LAW 103-43

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## **NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research**

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# **NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research**

## **INTRODUCTION**

This document sets forth guidelines on the inclusion of women and members of minority groups and their subpopulations in clinical research, including clinical trials, supported by the National Institutes of Health (NIH). For the purposes of this document, clinical research is defined as NIH-supported biomedical and behavioral research involving human subjects. These guidelines, implemented in accordance with section 492B of the Public Health Service Act, added by the NIH Revitalization Act of 1993, Public Law (Pub.L.) 103-43, supersede and strengthen the previous policies, NIH/ADAMHA Policy Concerning the Inclusion of Women in Study Populations, and ADAMHA/NIH Policy Concerning the Inclusion of Minorities in Study Populations, published in the NIH GUIDE FOR GRANTS AND CONTRACTS, 1990.

The 1993 guidelines continue the 1990 guidelines with three major additions. The new policy requires that, in addition to the continuing inclusion of women and members of minority groups in all NIH-supported biomedical and behavioral research involving human subjects, the NIH must:

- Ensure that women and members of minorities and their subpopulations are included in all human subject research;
- For Phase III clinical trials, ensure that women and minorities and their subpopulations must be included such that valid analyses of differences in intervention effect can be accomplished;
- Not allow cost as an acceptable reason for excluding these groups; and,
- Initiate programs and support for outreach efforts to recruit these groups into clinical studies.

Since a primary aim of research is to provide scientific evidence leading to a change in health policy or a standard of care, it is imperative to determine whether the intervention or therapy being studied affects women or men or members of minority groups and their subpopulations differently. To this end, the guidelines published here are intended to ensure that all future NIH-supported biomedical and behavioral research involving human subjects will be carried out in a manner sufficient to elicit information about individuals of both genders and the diverse racial and ethnic groups and, in the case of clinical trials, to examine differential effects on such groups. Increased attention, therefore, must be given to gender, race, and ethnicity in earlier stages of research to allow for informed decisions at the Phase III clinical trial stage.

These guidelines reaffirm NIH's commitment to the fundamental principles of inclusion of women and racial and ethnic minority groups and their subpopulations in research. This policy should result in a variety of new research opportunities to address significant gaps in knowledge about health problems that affect women and racial/ethnic minorities and their subpopulations.

The NIH recognizes that issues will arise with the implementation of these guidelines and thus welcomes comments. During the first year of implementation, NIH will review the comments, and consider modifications, within the scope of the statute, to the guidelines.

## **BACKGROUND**

The NIH Revitalization Act of 1993, PL 103-43, signed by President Clinton on June 10, 1993, directs the NIH to establish guidelines for inclusion of women and minorities in clinical research. This guidance shall include guidelines regarding:

- (A) the circumstances under which the inclusion of women and minorities as subjects in projects of clinical research is inappropriate...;
- (B) the manner in which clinical trials are required to be designed and carried out...; and
- (C) the operation of outreach programs... 492B(d)(1).

The statute states that:

In conducting or supporting clinical research for the purposes of this title, the Director of NIH shall... insure that -

- A. women are included as subjects in each project of such research; and
- B. members of minority groups are included in such research. 492B(a)(1).

The statute further defines "clinical research" to include "clinical trials" and states that:

In the case of any clinical trial in which women or members of minority groups will be included as subjects, the Director of NIH shall ensure that the trial is designed and carried out in a manner sufficient to provide for valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial. 492B(C)

Specifically addressing the issue of minority groups, the statute states that:

The term "minority group" includes subpopulations of minority groups. The Director of NIH shall, through the guidelines established...define the terms "minority group" and "subpopulation" for the purposes of the preceding sentence. 492 B(g)(2)

The statute speaks specifically to outreach and states that:

The Director of NIH, in consultation with the Director of the Office of Research of Women's Health and the Director of the Office of Research on Minority Health, shall conduct or support outreach programs for the recruitment of women and members of minority groups as subjects in the projects of clinical research. 492B(a)(2)

The statute includes a specific provision pertaining to the cost of clinical research and, in particular, clinical trials:

(A) (i) In the case of a clinical trial, the guidelines shall provide that the costs of such inclusion in the trial is (sic) not a permissible consideration in determining whether such inclusion is inappropriate. 492B(d)(2)

(ii) In the case of other projects of clinical research, the guidelines shall provide that the costs of such inclusion in the project is (sic) not a permissible consideration in determining whether such inclusion is inappropriate unless the data regarding women or members of minority groups, respectively, that would be obtained in such project (in the event that such inclusion were required) have been or are being obtained through other means that provide data of comparable quality. 492B(d)(2)

Exclusions to the requirement for inclusion of women and minorities are stated in the statute, as follows:

The requirements established regarding women and members of minority groups shall not apply to the project of clinical research if the inclusion, as subjects in the project, of women and members of minority groups, respectively -

- (1) is inappropriate with respect to the health of the subjects;
  - (2) is inappropriate with respect to the purpose of the research; or
  - (3) is inappropriate under such other circumstances as the Director of NIH may designate.
- 492B(b)

(B) In the case of a clinical trial, the guidelines may provide that such inclusion in the trial is not required if there is substantial scientific data demonstrating that there is no significant difference between -

- (i) the effects that the variables to be studied in the trial have on women or members of minority groups, respectively; and
- (ii) The effects that variables have on the individuals who would serve as subjects in the trial in the event that such inclusion were not required. 492(b)(d)(2)

## **POLICY**

### **Research Involving Human Subjects**

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an Institute/Center Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants.

### **NIH Phase III Clinical Trials**

Under the statute, when an NIH defined Phase III clinical trial (see Definitions, Section V-A) is proposed, evidence must be reviewed to show whether or not clinically important sex/gender and/or race/ethnicity differences in the intervention effect are to be expected. This evidence may include, but is not limited to, data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies.

The policy section of these Guidelines will be cited in the terms and conditions of all awards for grants, cooperative agreements and contracts supporting NIH Phase III clinical trials.

Investigators must consider the following when planning, conducting, and reporting an NIH Defined Phase III clinical trial. Based on prior studies, one of the three situations below will apply:

#### **1. Prior Studies Support the Existence of Significant Differences.**

If the data from prior studies strongly support the existence of significant differences of clinical or public health importance in intervention effect among subgroups (sex/gender and/or racial/ethnic subgroups), the primary question(s) to be addressed by the proposed NIH Phase III clinical trial and the design of that trial must specifically accommodate this. For example, if men and women are thought to respond differently to an intervention, then the Phase III clinical trial must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for each.

The Research Plan in the application or proposal must include a description of plans to conduct analyses to detect significant differences in intervention effect. The final protocol approved by the Institutional Review Board (IRB) must include these plans for analysis. The award will require that the results of subset analyses must be reported to NIH in Progress Reports, Competitive Renewal Application (or Contract Renewals/Extensions), and in the required Final Progress Report.

Inclusion of the results of subset analyses is strongly encouraged in all publication submissions. If the analysis reveals no subset differences, a brief statement to that effect, indicating the subsets analyzed, will suffice.

#### **2. Prior Studies Support No Significant Differences**

If the data from prior studies strongly support no significant differences of clinical or public health importance in intervention effect between subgroups, then sex/gender and/or race/ethnicity will not

be required as subject selection criteria. However, the inclusion and analysis of sex/gender and/or racial/ethnic subgroups is still strongly encouraged.

### 3. Prior Studies Neither Support nor Negate Significant Differences

If the data from prior studies neither support strongly nor negate strongly the existence of significant differences of clinical or public health importance in intervention effect between subgroups, then the Phase III trial will be required to include sufficient and appropriate entry of gender and racial/ethnic subgroups, so that valid analysis of the intervention effect in subgroups can be performed. However, the trial will not be required to provide high statistical power for each subgroup.

The Research Plan in the application or proposal must include a description of plans to conduct the valid analyses of the intervention effect in subgroups. The final protocol approved by the IRB must include these plans for analysis. The award will require that the results of subset analyses must be reported to NIH in Progress Reports, Competitive Renewal Applications (or Contract Renewals/Extensions), and in the required Final Progress Report.

Inclusion of the results of subset analyses is strongly encouraged in all publication submissions. If the analysis reveals no subset differences, a brief statement to that effect, indicating the subsets analyzed, will suffice.

### **Funding**

NIH funding components will not award any grant, cooperative agreement, or contract or support any intramural project to be conducted or funded in Fiscal Year 1995 and thereafter which does not comply with this policy. For research awards that are covered by this policy, awardees will report annually on enrollment of women and men, and on the race and ethnicity of research participants.

## **IMPLEMENTATION**

### **Date of Implementation**

This policy applies to all applications/proposals and intramural projects to be submitted on and after June 1, 1994 (the date of full implementation) seeking Fiscal Year 1995 support. Projects funded prior to June 10, 1993, must still comply with the 1990 policy and report annually on enrollment of subjects using gender and racial/ethnic categories as required in the Application for Continuation of a Public Health Service Grant (PHS Form 2590), in contracts and in intramural projects.

### **Transition Policy**

NIH-supported biomedical and behavioral research projects involving human subjects, with the exception of Phase III clinical trial projects as discussed below, that are awarded between June 10, 1993, the date of enactment, and September 30, 1994, the end of Fiscal Year 1994, shall be subject to the requirements of the 1990 policy and the annual reporting requirements on enrollment using gender and racial/ethnic categories.

For all Phase III clinical trial projects proposed between June 10, 1993 and September 30, 1994, Institute/Center staff will examine the applications/proposals, pending awards, awards and intramural projects to determine if the study was developed in a manner consistent with the new guidelines. If it is deemed inconsistent, NIH staff will contact investigators to discuss approaches to accommodate the new policy. Administrative actions may be needed to accommodate or revise the pending trials. Institutes/Centers may need to consider initiating a complementary activity to address any gender or minority representation concerns.

The NIH Director will determine whether the Phase III clinical trial being considered during this transition is in compliance with this policy, whether acceptable modifications have been made, or whether the Institute/Center will initiate a complementary activity that addresses the gender or minority representation concerns. Pending awards will not be funded without this determination.

Solicitations issued by the NIH planned for release after the date of publication of the guidelines in the ***Federal Register*** will include the new requirements.

### **Roles and Responsibilities**

While this policy applies to all applicants for NIH-supported biomedical and behavioral research involving human subjects, certain individuals and groups have special roles and responsibilities with regard to the adoption and implementation of these guidelines.

The NIH staff will provide educational opportunities for the extramural and intramural community concerning this policy; monitor its implementation during the development, review, award, and conduct of research; and manage the NIH research portfolio to address the policy.

**Principal Investigators:** Principal investigators should assess the theoretical and/or scientific linkages between gender, race/ethnicity, and their topic of study. Following this assessment, the principal investigator and the applicant institution will address the policy in each application and proposal, providing the required information on inclusion of women and minorities and their subpopulations in research projects, and any required justifications for exceptions to the policy. Depending on the purpose of the study, NIH recognizes that a single study may not include all minority groups.

**Institutional Review Boards (IRBs):** As the IRBs implement the guidelines described herein for the inclusion of women and minorities and their subpopulations, they must also implement the regulations for the protection of human subjects as described in title 45 CFR part 46, "Protection of Human Subjects." They should take into account the Food and Drug Administration's "Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs," Vol. 58 ***Federal Register*** 39406.

**Peer Review Groups:** In conducting peer review for scientific and technical merit, appropriately constituted initial review groups (including study sections), technical evaluation groups, and intramural review panels will be instructed as follows:

- To evaluate the proposed plan for the inclusion of minorities and both genders for appropriate representation or to evaluate the proposed justification when representation is limited or absent,
- To evaluate the proposed exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the health of the subjects,
- To evaluate the proposed exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the purpose of the research,
- To determine whether the design of clinical trials is adequate to measure differences when warranted,
- To evaluate the plans for recruitment/outreach for study participants, and
- To include these criteria as part of the scientific assessment and assigned score.

**NIH Advisory Councils:** In addition to its current responsibilities for review of projects where the peer review groups have raised questions about the appropriate inclusion of women and minorities, the Advisory Council/Board of each Institute/Center shall prepare biennial reports, for inclusion in the overall NIH Director's biennial report, describing the manner in which the Institute/Center has complied with the provisions of the statute.

**Institute/Center Directors:** Institute/Center Directors and their staff shall determine whether: (a) the research involving human subjects, (b) the Phase III clinical trials, and (c) the exclusions meet the requirements of the statute and these guidelines.

**NIH Director:** The NIH Director may approve, on a case-by-case basis, the exclusion of projects, as recommended by the Institute/Center Director, that may be inappropriate to include within the

requirements of these guidelines on the basis of circumstances other than the health of the subjects, the purpose of the research, or costs.

**Recruitment Outreach by Extramural and Intramural Investigators:** Investigators and their staff(s) are urged to develop appropriate and culturally sensitive outreach programs and activities commensurate with the goals of the study. The objective should be to actively recruit the most diverse study population consistent with the purposes of the research project. Indeed, the purpose should be to establish a relationship between the investigator(s) and staff(s) and populations and community(ies) of interest such that mutual benefit is derived for participants in the study. Investigator(s) and staff(s) should take precautionary measures to ensure that ethical concerns are clearly noted, such that there is minimal possibility of coercion or undue influence in the incentives or rewards offered in recruiting into or retaining participants in studies. It is also the responsibility of the IRBs to address these ethical concerns.

Furthermore, while the statute focuses on recruitment outreach, NIH staff underscore the need to appropriately retain participants in clinical studies, and thus, the outreach programs and activities should address both recruitment and retention.

To assist investigators and potential study participants, NIH staff have prepared a notebook, "NIH Outreach Notebook On the Inclusion of Women and Minorities in Biomedical and Behavioral Research." The notebook addresses both recruitment and retention of women and minorities in clinical studies, provides relevant references and case studies, and discusses ethical issues. It is not intended as a definitive text on this subject, but should assist investigators in their consideration of an appropriate plan for recruiting and retaining participants in clinical studies.

**Educational Outreach by NIH to Inform the Professional Community:** NIH staff will present the new guidelines to investigators, IRB members, peer review groups, and Advisory Councils in a variety of public educational forums.

### **Applicability to Foreign Research Involving Human Subjects**

For foreign awards, the NIH policy on inclusion of women in research conducted outside the U.S. is the same as that for research conducted in the U.S.

However, with regard to the population of the foreign country, the definition of the minority groups may be different than in the U.S. If there is scientific rationale for examining subpopulation group differences within the foreign population, investigators should consider designing their studies to accommodate these differences.

## **DEFINITIONS**

Throughout the section of the statute pertaining to the inclusion of women and minorities, terms are used which require definition for the purpose of implementing these guidelines. These terms, drawn directly from the statute, are defined below.

### **NIH Defined Clinical Trial**

For the purpose of these guidelines, an NIH defined "clinical trial" is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

### **Research Involving Human Subjects**

All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research under this policy. Under this policy, the definition of human subjects in title 45 CFR part 46, the Department of Health and Human Services regulations for the protection of human subjects applies: "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." These regulations specifically address the protection of human subjects from research risks. It should be noted that there are research areas (Exemptions 1-6) that are exempt from these regulations. However, under these guidelines, NIH-supported biomedical and behavioral research projects involving human subjects which are exempt from the human subjects regulations should still address the inclusion of women and minorities in their study design. Therefore, all biomedical and behavioral research projects involving human subjects will be evaluated for compliance with this policy.

### **Valid Analysis**

The term "valid analysis" means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are:

- Allocation of study participants of both sexes/genders (males and females) and from different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization,
- Unbiased evaluation of the outcome(s) of study participants, and
- Use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the sex/gender and racial/ethnic groups.

### **Significant Difference**

For purposes of this policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

### **Racial and Ethnic Categories**

**Minority Groups:** A minority group is a readily identifiable subset of the U.S. population which is distinguished by either racial, ethnic, and/or cultural heritage.

The Office of Management and Budget (OMB) Directive No. 15 defines the minimum standard of basic racial and ethnic categories, which are used below. NIH has chosen to continue the use of these definitions because they allow comparisons to many national data bases, especially national health data bases. Therefore, the racial and ethnic categories described below should be used as basic guidance, cognizant of the distinction based on cultural heritage.

*American Indian or Alaskan Native*--a person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition.

*Asian or Pacific Islander*--a person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands. This area includes, for example, China, India, Japan, Korea, the Philippine Islands and Samoa.

*Black, not of Hispanic Origin*--a person having origins in any of the black racial groups of Africa.



*Hispanic*--a person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race.

Majority Groups:

*White, not of Hispanic Origin*--a person having origins in any of the original peoples of Europe, North Africa, or the Middle East.

NIH recognizes the diversity of the U.S. population and that changing demographics are reflected in the changing racial and ethnic composition of the population. The terms "minority groups" and "minority subpopulations" are meant to be inclusive, rather than exclusive, of differing racial and ethnic categories.

Subpopulations: Each minority group contains subpopulations which are delimited by geographic origins, national origins and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific racial and ethnic origin. Attention to subpopulations also applies to individuals of mixed racial and/or ethnic parentage. Researchers should be cognizant of the possibility that these racial/ethnic combinations may have biomedical and/or cultural implications related to the scientific question under study.

### **Outreach Strategies**

These are outreach efforts by investigators and their staff(s) to appropriately recruit and retain populations of interest into research studies. Such efforts should represent a thoughtful and culturally sensitive plan of outreach and generally include involvement of other individuals and organizations relevant to the populations and communities of interest, e.g., family, religious organizations, community leaders and informal gatekeepers, and public and private institutions and organizations. The objective is to establish appropriate lines of communication and cooperation to build mutual trust and cooperation such that both the study and the participants benefit from such collaboration.

### **Research Portfolio**

Each Institute and Center at the NIH has its own research portfolio, i.e., its "holdings" in research grants, cooperative agreements, contracts and intramural studies. The Institute or Center evaluates the research awards in its portfolio to identify those areas where there are knowledge gaps or which need special attention to advance the science involved. NIH may consider funding projects to achieve a research portfolio reflecting diverse study populations. With the implementation of this new policy, there will be a need to ensure that sufficient resources are provided within a program to allow for data to be developed for a smooth transition from basic research to Phase III clinical trials that meet the policy requirements.

## **DISCUSSION—ISSUES IN SCIENTIFIC PRINCIPLES AND STUDY**

### **Issues in Research Involving Human Subjects**

The biomedical and behavioral research process can be viewed as a stepwise process progressing from discovery of new knowledge through research in the laboratory, research involving animals, research involving human subjects, validation of interventions through clinical trials and broad application to improve the health of the public.

All NIH-supported biomedical and behavioral research involving human subjects is defined broadly in this guidance as clinical research. This is broader than the definition provided in the 1990 NIH Guidance and in many program announcements, requests for applications, and requests for proposals since 1990.

The definition was broadened because of the need to obtain data about minorities and both genders early in the research process when hypotheses are being formulated, baseline data are being collected, and various measurement instruments and intervention strategies are being developed. Broad inclusion at these early stages of research provides valuable information for designing broadly based clinical trials, which are a subset of studies under the broad category of research studies.

The policy on inclusion of minorities and both genders applies to all NIH-supported biomedical and behavioral research involving human subjects so that the maximum information may be obtained to understand the implications of the research findings on the gender or minority group.

Investigators should consider the types of information concerning gender and minority groups which will be required when designing future Phase III clinical trials, and try to obtain it in their earlier stages of research involving human subjects. NIH recognizes that the understanding of health problems and conditions of different U.S. populations may require attention to socioeconomic differences involving occupation, education, and income gradients.

### **Issues in Clinical Trials**

The statute requires appropriate representation of subjects of different gender and race/ethnicity in clinical trials so as to provide the opportunity for detecting major qualitative differences (if they exist) among gender and racial/ethnic subgroups and to identify more subtle differences that might, if warranted, be explored in further specifically targeted studies. Other interpretations may not serve as well the health needs of women, minorities, and all other constituencies.

Preparatory to any Phase III clinical trial, certain data are typically obtained. Such data are necessary for the design of an appropriate Phase III trial and include observational clinical study data, basic laboratory (i.e., *in vitro* and animal) data, and clinical, physiologic, pharmacokinetic, or biochemical data from Phase I and Phase II studies. Genetic studies, behavioral studies, and observational, natural history, and epidemiological studies may also contribute data.

It is essential that data be reviewed from prior studies on a diverse population, that is, in subjects of both genders and from different racial/ethnic groups. These data must be examined to determine if there are significant differences of clinical or public health importance observed between the subgroups.

While data from prior studies relating to possible differences among intervention effects in different subgroups must be reviewed, evidence of this nature is likely to be less convincing than that deriving from the subgroup analyses that can be performed in usual-sized Phase III trials. This is because the evidence from preliminary studies is likely to be of a more indirect nature (e.g., based on surrogate endpoints), deriving from uncontrolled studies (e.g., non-randomized Phase II trials), and based on smaller numbers of subjects than in Phase III secondary analyses. For this reason, it is likely that data from preliminary studies will, in the majority of cases, neither clearly reveal significant differences of clinical or public health importance between subgroups of patients, nor strongly negate them.

In these cases, Phase III trials should still have appropriate gender and racial/ethnic representation, but they would not need to have the large sample sizes necessary to provide a high statistical power for detecting differences in intervention effects among subgroups. Nevertheless, analyses of subgroup effects must be conducted and comparisons between the subgroups must be made. Depending on the results of these analyses, the results of other relevant research, and the results of meta-analyses of clinical trials, one might initiate subsequent trials to examine more fully these subgroup differences.

### **Issues Concerning Appropriate Gender Representation**

The "population at risk" may refer to only one gender where the disease, disorders, or conditions are gender specific. In all other cases, there should be approximately equal numbers of both sexes in studies of populations or subpopulations at risk, unless different proportions are appropriate because of the known prevalence, incidence, morbidity, mortality rates, or expected intervention effect.

### **Issues Concerning Appropriate Representation of Minority Groups and Subpopulations in All Research Involving Human Subjects Including Phase III Clinical Trials**

While the inclusion of minority subpopulations in research is a complex and challenging issue, it nonetheless provides the opportunity for researchers to collect data on subpopulations where knowledge gaps exist. Researchers must consider the inclusion of subpopulations in all stages of research design. In meeting this objective, they should be aware of concurrent research that addresses specific

subpopulations, and consider potential collaborations which may result in complementary subpopulation data.

At the present time, there are gaps in baseline and other types of data necessary for research involving certain minority groups and/or subpopulations of minority groups. In these areas, it would be appropriate for researchers to obtain such data, including baseline data, by studying a single minority group.

It would also be appropriate for researchers to test survey instruments, recruitment procedures, and other methodologies used in the majority or other population(s) with the objective of assessing their feasibility, applicability, and cultural competence/relevance to a particular minority group or subpopulation.

This testing may provide data on the validity of the methodologies across groups. Likewise, if an intervention has been tried in the majority population and not in certain minority groups, it would be appropriate to assess the intervention effect on a single minority group and compare the effect to that obtained in the majority population. These types of studies will advance scientific research and assist in closing knowledge gaps.

A complex issue arises over how broad or narrow the division into different subgroups should be, given the purpose of the research. Division into many racial/ethnic subgroups is tempting in view of the cultural and biological differences that exist among these groups and the possibility that some of these differences may in fact impact in some way upon the scientific question. Alternatively, from a practical perspective, a limit has to be placed on the number of such subgroups that can realistically be studied in detail for each intervention that is researched. The investigator should clearly address the rationale for inclusion or exclusion of subgroups in terms of the purpose of the research. Emphasis should be placed upon inclusion of subpopulations in which the disease manifests itself or the intervention operates in an appreciable different way. Investigators should report the subpopulations included in the study.

An important issue is the appropriate representation of minority groups in research, especially in geographical locations which may have limited numbers of racial/ethnic population groups available for study. The investigator must address this issue in terms of the purpose of the research and other factors, such as the size of the study, relevant characteristics of the disease, disorder or condition, and the feasibility of making a collaboration or consortium or other arrangements to include minority groups. A justification is required if there is limited representation. Peer reviewers and NIH staff will consider the justification in their evaluations of the project.

NIH interprets the statute in a manner that leads to feasible and real improvements in the representation of different racial/ethnic groups in research and places emphasis on research in those subpopulations that are disproportionately affected by certain diseases or disorders.

**APPENDIX G: Guideline for the Study and Evaluation of Gender  
Differences in the Clinical Evaluation of Drugs**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

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## **Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs**

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# **Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs**

## **Introduction**

The Food and Drug Administration (FDA) advises that this guideline represents its current position on the clinical evaluation of drugs in humans. This guideline does not bind the agency, and it does not react or confer any rights, privileges, or benefits for or on any person.

The principles of inclusion of women in product development programs and analysis of subgroup differences outlined in this guideline also apply to the clinical development of biological products and medical devices.

## **Abstract**

In general, drugs should be studied prior to approval in subjects representing the full range of patients likely to receive the drug once it is marketed. Although in most cases, drugs behave qualitatively similarly in demographic (age, gender, race) and other (concomitant illness, concomitant drugs) subsets of the population, there are many quantitative differences, for example, in dose-response, maximum size of effect, or in the risk of an adverse effect. Recognition of these differences can allow safer and more effective use of drugs. Rarely, there may be qualitative differences as well. It is very difficult to evaluate subsets of the overall population as thoroughly as the entire population, but sponsors are expected to include a full range of patients in their studies, carry out appropriate analyses to evaluate potential subset differences in the patients they have studied, study possible pharmacokinetic differences in patient subsets, and carry out targeted studies to look for subset pharmacodynamic differences that are especially probable, are suggested by existing data, or that would be particularly important if present. Study protocols are also expected to provide appropriate precautions against exposure of fetuses to potentially dangerous agents. Where animal data suggest possible effects on fertility, such as decreased sperm production, special studies in humans may be needed to evaluate this potential toxicity.

## **Underlying Observations**

The following general observations and conclusions underlie the recommendations set forth in this guideline:

1. Variations in response to drugs, including gender-related differences, can arise from pharmacokinetic differences (that is, differences in the way a drug is absorbed, excreted, metabolized, or distributed) or pharmacodynamic differences (i.e., differences in the pharmacologic or clinical response to a given concentration of the drug in blood or other tissue).
2. Gender-related variations in drug effects may arise from a variety of sources. Some of these are specifically associated with gender, e.g., effects of endogenous and exogenous hormones. Gender-related differences could also arise, however, not because of gender itself, but because the frequency of a particular characteristic (for example, small size, concomitant hepatic disease or concomitant drug treatment, or habits such as smoking or alcohol use) is different in one gender, even if the characteristic could occur in either gender. Proper management of patients of both genders thus requires that physicians know all the factors that can influence the pharmacokinetics of a drug. An approach is needed that will identify, better than is done at present, all such factors. Understanding how various factors may influence pharmacokinetics will greatly enhance our ability to treat people of both genders appropriately.
3. For a number of practical and theoretical reasons, the evaluation of possible gender-related differences in response should focus initially on the evaluation of potential pharmacokinetic differences. Such differences are known to occur and have, at least to date, been documented much more commonly than documented pharmacodynamic differences. Moreover, pharmacokinetic differences are relatively easy to discover. Once reliable assays are developed for a drug and its metabolites (such assays are now almost always available early in the development of the drug), techniques exist for readily assessing gender-related or other subgroup-related pharmacokinetic differences.

Formal pharmacokinetic studies are one means of answering questions about specific subgroups. Another approach is use of a screening procedure, a "pharmacokinetic screen" (see "Guidelines for the

Study of Drugs Likely to be Used in the Elderly"). Carried out in phase 2 and 3 study populations, the pharmacokinetic screen can greatly increase the ability to detect pharmacokinetic differences in subpopulations and individuals, even when these differences are not anticipated. By obtaining a small number of blood concentration determinations in most or all phase 2 and 3 patients, it is possible to detect markedly atypical pharmacokinetic behavior in individuals, such as that seen in slow metabolizers of debrisoquin, and pharmacokinetic differences in population subsets, such as patient populations of different gender, age, or race, or patients with particular underlying diseases or concomitant therapy. The screen may also detect interactions of two factors, e.g., gender and age. The relative ease with which pharmacokinetic differences among population subsets can be assessed contrasts with the difficulty of developing precise relationships of most clinical responses to drug dose or to the drug concentration in blood, which usually would be necessary when attempting to observe pharmacodynamic differences between two subgroups.

A final reason to emphasize pharmacokinetic evaluation is that it must be carried out to allow relevant assessment of pharmacodynamic differences or relationships. Assessing pharmacodynamic differences between groups or establishing blood concentration-response relationships is possible only when groups are reasonably well matched for blood concentrations. Enough pharmacokinetic data must therefore be available to permit the investigator to administer doses that will produce comparable blood concentrations in the subsets to be compared or, alternatively, to compare subsets that have been titrated to similar blood concentrations.

4. The number of documented gender-related pharmacodynamic differences of clinical consequence is at this time small, and conducting formal pharmacodynamic/effectiveness studies to detect them may be difficult, depending on the clinical endpoint. Such studies are therefore not routinely necessary. The by-gender analyses of clinical trials that include both men and women, however, which are specified in the 1988 guideline entitled "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" are not difficult to carry out. Particularly if these analyses are accompanied by blood concentration data for each patient, they can detect important pharmacodynamic/effectiveness differences related to gender.

#### **Inclusion of Both Genders in Clinical Studies**

The patients included in clinical studies should, in general, reflect the population that will receive the drug when it is marketed. For most drugs, therefore, representatives of both genders should be included in clinical trials in numbers adequate to allow detection of clinically significant gender-related differences in drug response. Although it may be reasonable to exclude certain patients at early stages because of characteristics that might make evaluation of therapy more difficult (e.g., patients on concomitant therapy), such exclusions should usually be abandoned as soon as possible in later development so that possible drug-drug and drug-disease interactions can be detected. Thus, for example, there is ordinarily no good reason to exclude women using oral contraceptives or estrogen replacement from trials. Rather, they should be included and differences in responses between them and patients not on such therapy examined. Pharmacokinetic interaction studies (or screening approaches) to look at the interactions resulting from concomitant treatment are also useful.

Ordinarily, patients of both genders should be included in the same trials. This permits direct comparisons of genders within the studies. In some cases, however, it may be appropriate to conduct studies in a single gender, e.g., to evaluate the effects of phases of the menstrual cycle on drug response.

Although clinical or pharmacokinetic data collected during phase 3 may provide evidence of gender-related differences, these data may become available too late to affect the design and dose-selection of the pivotal controlled trials. Inclusion of women in the earliest phases of clinical development, particularly in early pharmacokinetic studies, is, therefore, encouraged so that information on gender differences may be used to refine the design of later trials. Note that the strict limitation on the participation of women of childbearing potential in phase 1 and early phase 2 trials that was imposed by the 1977 guideline entitled, "General Considerations for the Clinical Evaluation of Drugs," has been eliminated.

There is no regulatory or scientific basis for routine exclusion of women from bioequivalence trials. For certain drugs, however, it is possible that changes during the menstrual cycle may lead to increases in

intra-subject variability. Such variability could be related to hormonally-mediated differences in metabolism or changes in fluid balance. Sponsors of bioequivalence trials are encouraged to examine available information on the pharmacokinetics and metabolism of the test drugs and related drugs to determine whether there is a basis for concern about variability in pharmacokinetics during the menstrual cycle. Where the available information does raise such concern, measures could be taken to reduce or adjust for variability, e.g., administration of each drug at the same phase of the menstrual cycle, or inclusion of larger numbers of subjects. Sponsors are encouraged to collect data that will contribute to the understanding of the relationship between hormonal variations and pharmacokinetics.

#### **Analysis of Effectiveness and Adverse Effects by Gender**

FDA's guidelines on the clinical and statistical sections of NDA's calls for analyses of effectiveness, adverse effects, dose-response, and, if available, blood concentration-response, to look for the influence of:

(1) demographic features, such as age, gender, and race; and (2) other patient characteristics, such as body size (body weight, lean body mass, fat mass), renal, cardiac, and hepatic status, the presence of concomitant illness, and concomitant use of drugs, including ethanol and nicotine. Analyses to detect the influence of gender should be carried out both for individual studies and in the overall integrated analyses of effectiveness and safety. Such analyses of subsets with particular characteristics can be expected to detect only relatively large gender-related differences, but in general, small differences are not likely to be clinically important. The results of these analyses may suggest the need for more formal dose-response or blood concentration-response studies in men or women or in other patient subsets. Depending on the magnitude of the findings, or their potential importance (e.g., they would be more important for drugs with low therapeutic indices), these additional studies might be carried out before or after marketing.

#### **Defining the Pharmacokinetics of the Drug in Both Genders**

The factors most commonly having a major influence on pharmacokinetics are renal function, for drugs excreted by the kidney, and hepatic function, for drugs that are metabolized or excreted by the liver: these should be assessed directly as part of the ordinary development of drugs. The pharmacokinetic effects of other subgroup characteristics such as gender can be assessed either by a pharmacokinetic screening approach, described in the 1989 guideline entitled, "Guideline for the Study of Drugs Likely to Be Used in the Elderly," or by formal pharmacokinetic studies in specific gender or age groups.

Using either a specific pharmacokinetic study or a pharmacokinetic screen, the pharmacokinetics of a drug should be defined for both genders. In general, it is prudent to at least carry out pilot studies to look for major pharmacokinetic differences before conducting definitive controlled trials, so that differences that might lead to the need for different dosing regimens can be detected. Such studies are particularly important for drugs with low therapeutic indices, where the smaller average size of women alone might be sufficient to require modified dosing, and for drugs with nonlinear kinetics, where the somewhat higher milligram per kilogram dose caused by a woman's smaller size could lead to much larger differences in blood concentrations of drug. Gender may interact with other factors, such as age. The potential for such interactions should be explored.

Three pharmacokinetic issues related specifically to women that should be considered during drug development are: (1) the influence of menstrual status on the drug's pharmacokinetics, including both comparisons of premenopausal and postmenopausal patients and examination of within-cycle changes; (2) the influence of concomitant supplementary estrogen treatment or systemic contraceptives (oral contraceptives, long-acting progesterone) on the drug's pharmacokinetics; and (3) the influence of the drug on the pharmacokinetics of oral contraceptives. Which of these influences should be studied in a given case would depend on the drug's excretion, metabolism, and other pharmacokinetic properties, and on the steepness of the dose-response curve.

Hormonal status during the menstrual cycle may affect plasma volume and the volume of distribution (and thus clearance) of drugs. The activity of certain cytochrome P450 enzymes may be influenced by estrogen levels and, in addition, microsomal oxidation by these enzymes may decline in the elderly more in men than women. Oral contraceptives can cause decreased clearance of drugs (e.g., imipramine,



diazepam, chlordiazepoxide, phenytoin, caffeine, and cyclosporine), apparently by inhibiting hepatic metabolism. They can also increase clearance by inducing drug metabolism (e.g., of acetaminophen, salicylic acid, morphine, lorazepam, temazepam, oxazepam, and clofibrate). Certain anticonvulsants (carbamazepine, phenytoin) and antibiotics (rifampin) can reduce the effectiveness of oral contraceptives. Many of the potential interactions of gender and gender-related characteristics (e.g., use of oral contraceptives) can be evaluated with the pharmacokinetic screen. In some cases, specific studies will be needed.

### **Gender-Specific Pharmacodynamic Studies**

Because documented demographic differences in pharmacodynamics appear to be relatively uncommon, it is not necessary to carry out separate pharmacodynamic/effectiveness studies in each gender routinely. Evidence of such differences should be sought, however, in the data from clinical trials by carrying out the by-gender analyses suggested in the guideline on the clinical and statistical sections of NDA's. These analyses of controlled trials involving both genders are probably more likely to detect differences than studies carried out entirely in one gender. Experience has shown that gender differences can be detected with such approaches.

If the by-gender analyses suggest gender-related differences, or if such differences would be particularly important, e.g., because of a low therapeutic index, additional formal studies to seek such differences between the blood level-responses curves of men and women should be conducted. Even in the absence of a particular concern based on the by-gender analyses, if there is a readily measured pharmacodynamic endpoint, such as blood pressure or rate of ventricular premature beats, and if there are good dose-response data for the overall population, it should be feasible to develop dose-response data from population subsets (e.g., both genders) in the critical clinical trials.

### **Precautions in Clinical Trials Including Women of Childbearing Potential**

Appropriate precautions should be taken in clinical studies to guard against inadvertent exposure of fetuses to potentially toxic agents and to inform subjects and patients of potential risk and the need for precautions. In all cases, the informed consent document and investigator's brochure should include all available information regarding the potential risk of fetal toxicity. If animal reproductive toxicity studies are complete, the results should be presented, with some explanation of their significance in humans. If these studies have not been completed, other pertinent information should be provided, such as a general assessment of fetal toxicity in drugs with related structures or pharmacologic effects. If no relevant information is available, the informed consent document should explicitly note the potential for fetal risk.

In general, it is expected that reproductive toxicity studies will be completed before there is large-scale exposure of women of childbearing potential, i.e., usually by the end of phase 2 and before any expanded access program is implemented.

Except in the case of trials intended for the study of drug effects during pregnancy, clinical protocols should also include measures that will minimize the possibility of fetal exposure to the investigational drug. These would ordinarily include providing for the use of a reliable method of contraception (or abstinence) for the duration of drug exposure (which may exceed the length of the study), use of pregnancy testing (beta HCG) to detect unsuspected pregnancy prior to initiation of study treatment, and timing of studies (easier with studies of short duration) to coincide with, or immediately follow, menstruation. Female subjects should be referred to a study physician or other counselor knowledgeable in the selection and use of contraceptive approaches.

### **Potential Effects on Fertility**

Where abnormalities of reproductive organs or their function (spermatogenesis or ovulation) have been observed in experimental animals, the decision to include patients of reproductive age in a clinical study should be based on a careful risk-benefit evaluation, taking into account the nature of the abnormalities, the dosage needed to induce them, the consistency of findings in different species, the severity of the illness being treated, the potential importance of the drug, the availability of alternative treatment, and the duration of therapy. Where patients of reproductive potential are included in studies of drugs showing reproductive toxicity in animals, the clinical studies should include appropriate monitoring and/or

laboratory studies to allow detection of these effects. Long-term follow-up will usually be needed to evaluate the effects of such drugs in humans.