IRB Guidelines

FEDERAL REGULATIONS

45 CFR 46, "Protection of Human Subjects"

- Subpart A -- Basic HHS Policy for Protection of Human Research Subjects
- Subpart B -- Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- Subpart C -- Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D -- Additional Protections for Children Involved as Subjects in Research

The Belmont Report

U.S. Food and Drug Administration (FDA)

- FDA Good Clinical Practice

IRB GUIDANCE

Click the links below to view each section.

- Informed Consent
- Waiver of Informed Consent
- Re-Consenting Study Subjects
- Confidentiality/Protected Health Information
- Adverse Event Reporting
- Advertisement and Recruitment
- Research Involving Stored Human Samples, Specimens, or Data
- Protocol Deviations/Non-Compliance
- Multi-Institutional Guidelines
- Women and Minorities in Study Populations

Informed Consent

The Process of Informed Consent:

Since research subjects have the right to withdraw from a study, consent is an ongoing process. It starts well before any forms are signed and continues until the subject's participation is complete. The informed consent process is different from the consent form. It involves meeting with a potential subject, outlining the nature of the study, the risks and benefits of, and alternatives to participation, and all other information necessary for the subject to make a considered decision whether or not to participate. Investigators are responsible for assessing that subjects understand the information provided and that individuals give voluntary consent, free from coercion or undue influence. The consent form formalizes the agreement to participate and should be designed to document the process. Obtaining informed consent is not just giving a prospective subject a consent form and getting it signed. If consent is to be informed, the subjects must truly understand the study. Subjects should be able to see what they are consenting to. To achieve understanding, potential subjects should not be presented information all at once or only at the last minute. Information must be comprehensible. Consent documents must be written, in non-technical language that can be understood by a layperson with no more than an eighth-grade education, and must include at least the elements outlined in 45 CFR 46.116(a)&(b) nd Appendix 1 of Clinical Center Medical Administrative Series (MAS) issuance M77-2, Subject: Informed Consent (PDF, 10/2/2011).

It is the responsibility of the Principal Investigator (PI) to ensure that informed consent is obtained. Written consent must be obtained by the PI, or by a PI-designated member of the research team who is knowledgeable about the protocol. Whenever consent is to be obtained by someone other than the PI or an Associate Investigator (AI) on the study, this must be approved by the IRB. The consent document must be signed and dated by (a) the subject or his/her LAR, (b) the PI or approved designee obtaining the consent, and (c) a witness who attests only to the validity of the signature (i.e., that the research subject actually signed the consent), not to the validity of the quality of the consent. Any adult other than the person obtaining or providing consent may be a witness to the signature.

NIH consent document form 2514-1, "Consent to Participate in a Clinical Research Study," is used for all research conducted at the NIH Clinical Center (CC). Form 2514-1 is available from the IRB Administrative Office, Branch Protocol Support Offices, or electronically from the NIH Clinical Center Homepage. NIH form 2514-1 also includes information in the boilerplate on the first and last pages. For consent documents used at the Clinical Center, changes to the boilerplate language should only be made with approval of the IRB, as well as the Office of Human Subjects Research (OHSR) or the Office of General Counsel (OGC).

Written consent documents shall be approved by the IRB along with the written research protocol or amendment. Subsequent to final approval by the IRB (as indicated by the signature of the IRB Chair/Deputy Chair on the NIH-1195) but before use by the investigator, the protocol and consent document are sent for review by the Office of Protocol Services (OPS), CC, as well as review and approval by the Associate Director for Clinical Research, CC. OPS affixes approval dates, amendment numbers/dates and expiration dates to the consent document. OPS then adds consents to the Intranet for access by NIH staff. These expiration dates/amendment letters cannot be changed except by OPS personnel with appropriate access. This assists investigators, study staff and the IRB in being certain that appropriate versions of the documents are in use.
Copies of the approved consent form will also be kept in the IRB files and the files of the CC OPS. Protocol consent documents are time limited, and must be signed and dated by the subject, parent(s), or legally authorized representative (LAR) within the date identified on the last page of the document.

For a minor to participate in research, permission must be obtained from parent(s), legal guardian(s), or other LAR and assent obtained from the child (if capable of giving assent as determined by the IRB). For minimal risk research or research involving greater than minimal risk but a prospect of direct benefit to the individual child, the permission and signature of one parent is generally sufficient, if approved by the IRB. This shall be documented in the IRB minutes at the time of initial review. For other IRB approved research with children (i.e., greater than minimal risk with no prospect of direct benefit), the permission and signature of both parents is required unless one parent is deceased, unknown, legally incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (45 CFR46.408(b)).

For research involving adults who are unable to provide their own consent, permission for research participation must be obtained from a legally authorized representative (LAR). Individuals designated as durable power of attorney for health care via the NIH-200 Advance Directive or other valid advance directive, or court appointed guardians are acceptable as LARs. Investigators are responsible for informing the LAR about the research as well as assessing his or her understanding and voluntariness. Subjects deemed unable to provide their own consent should be so informed. Refer to M87-4, Subject: Research Involving Adults Who Are or May Be Unable to Consent (PDF, 5/19/2011), for requirements regarding adults with limited capacity to consent.

For research protocols or any procedures performed for the purposes of research that involve obtaining consent via technology and/or electronic process rather than in person, the procedures for obtaining consent, including how information will be transmitted and documented and by whom, shall be detailed in the written protocol. Review and approval must first be obtained from the Institute Clinical Director and the IRB.

All investigators should review and be familiar with the requirements for informed consent as outlined by Clinical Center Medical Administrative Series (MAS) issuance M77-2, Subject: Informed Consent (PDF, 10/21/2011); M92-5, Subject: Research Involving Children and Children's Assent to Research (PDF, 05/29/2012); and M87-4, Subject: Research Involving Adults Who Are or May Be Unable to Consent (PDF, 5/19/2011) for requirements regarding adults with limited capacity to consent.

Waiver of Informed Consent

In certain circumstances prescribed by the Federal regulations (45 CFR 46), an IRB may waive the requirement to obtain informed consent, or may approve a consent process which alters or does not include some of the elements of informed consent. Only the IRB can waive or modify the consent process. Researchers are not authorized to make this decision.

Re-Consenting Study Subjects

Any time the IRB requests or approves changes to consent documents, it must also determine whether or not study subjects currently enrolled on the studies under consideration must be re-consented.

Re-consenting of study subjects currently enrolled can occur in those circumstances when the protocol and the accompanying informed consent document are amended to include additional risks or other important new information. For example, new significant risks might be identified. In reaching a decision on whether additional risks are "significant", the IRB will consider: 1) what procedures are taking place during the course of the study; 2) how those procedures are being performed; and 3) at what point in the course of study it would no longer become necessary to re-consent the study subject. Re-consenting of study subjects who have completed active participation is at the discretion of the IRB. The IRB may decide to re-consent all, some, or none of these study subjects.

Should the IRB declare that re-consenting study subjects is necessary, it will be communicated in writing to the investigator. The investigator or designee will be required to make contact with study subjects prior to the next scheduled visit, and the study subject must be re-consented at the next visit. Verbal re-consent will not be permitted by the IRB.

Confidentiality/Protected Health Information

Certificates of Confidentiality:

The NIH has updated their policy for issuing Certificates of Confidentiality for NIH funded research, which applies to all of our clinical studies reviewed by the IRB.

Effective October 1, 2017, all research that was commenced or ongoing on or after December 13, 2016 and is within the scope of the Policy is deemed to be issued a Certificate through this Policy and is therefore required to protect the privacy of individuals who are subjects of such research in accordance with subsection 301(d) of the Public Health Service Act. Institutions and their investigators are responsible for determining whether research they conduct is subject to this Policy and therefore issued a Certificate. Certificates issued in this manner will not be issued as a separate document.

Previously, NIH provided these protections through the issuance of Certificates only upon receipt and approval of an application. However, in order to comply with the requirement in subsection 301(d) of the Public Health Service Act to minimize the burden to researchers, streamline the process, and reduce the time it takes to comply with the requirements associated with applying for a Certificate, NIH will now provide Certificates automatically to any NIH-funded recipients conducting research applicable to this Policy.

For studies in which informed consent is sought, NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.
Please see the following link for complete information about this and your obligations as an investigator: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html.

NIH Certificates of Confidentiality Kiosk (Page Last Updated: 10/01/2017)
- 18 Personal Identifiers That Are Considered Protected Health Information (PDF)

Expedited Reporting of Unanticipated Problems and Deaths:
The PI will report to the NCI-IRB:
- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received by the NCI-IRB within 7 days of PI awareness via iRIS. For confidentiality reasons, PIs should remove names, addresses, social security numbers, and any other identifying information from any supplemental information submitted with the form. Study numbers are the only identifiers that should be used.

Continuing Review Reporting Requirements:
For reporting of adverse events at time of continuing review, the NCI-IRB requires a summary report of adverse events that have occurred on the protocol since the previous continuing review and in aggregate. The method of presentation should provide the NCI-IRB with the information necessary to clearly identify risks to participants and to make a risk:benefit determination. Please sort the events by the system organ class and by grade. The summary report is based on the following guidance: any unexpected severity and/or unexpected frequency of expected events needs to be reported and interpreted in relation to the risk:benefit of study participants in the narrative. In addition, the protocol PI will report to the NCI-IRB:
- A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
- A summary of any instances of non-compliance.
- A tabular summary of the following adverse events:
  - All Grade 2 unexpected events that are possibly, probably or definitely related to the research;
  - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
  - All Grade 5 events regardless of attribution;
  - All Serious Events regardless of attribution.
  - **NOTE:** Grade 1 events are not required to be reported.

Memo: Reporting of Death Due to Progressive Disease as a Serious Adverse Event (PDF, 1/21/2009)

Advertisement and Recruitment
Advertisements are part of the informed consent and subject selection process. All advertisements, such as flyers, newspaper ads, radio and television announcements, bulletin board tear-offs, and posters, along with an explanation of other methods of recruiting subjects, must be submitted to and approved by the IRB. When advertisements are to be taped for broadcast, the IRB should review the final audio/video tape.

Advertisements should be submitted with the initial review application or as soon as the PI decides to use them. The content of advertisements should be limited to:
- The name and address of the PI;
- Purpose of the research;
- General eligibility criteria;
- A straightforward and truthful description of benefits;
- The time or other commitment required of the subjects; and
- The location of the research and the person or office to contact for further information.

Advertisements should not claim, explicitly or implicitly, that the research is treatment or is superior to any current practice. Extravagant attention-getting devices such as extremely large bold typefaces and dollar signs are prohibited. Advertisements should not pressure readers to participate. Advertisements should not use terms such as “new treatment,” “new medication,” or “new drug” without explaining that the test article is investigational. A phrase such as “receive new treatments” leads subjects to believe they will be receiving newly improved products of proven worth. Advertisements should not promise “free medical treatment” when the intent is only to say subjects will not be charged for taking part in the investigation.

IRB review and approval of listings of clinical trials on the internet would provide no additional safeguard and is not required when the system format limits the information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information. However, when the opportunity to add additional descriptive information is not precluded by the
**Research Involving Stored Human Samples, Specimens, or Data**

If you are conducting research that involves stored human specimens, samples, or data, please carefully read the following:

- **DHHS Requirement for Continued IRB Oversight of All Human Subjects Research (Word, 6/12/2006)**
- **NIH Information Sheet 14: NIH Requirements for the Research Use of Stored Human Specimens and Data (Word, 6/12/2006)**

Research involving stored identified or coded specimens or data, when Intramural Research Program (IRP) investigators can identify the sources, must receive prospective and continuing NIH IRB approval. Any activities that are not consistent with this requirement must stop until NIH IRB approval is granted.

Please note that human subjects research at the NIH must be in compliance with the requirements set forth in the above documents.

**Protocol Deviations and Non-Compliance**

**Definition:**

**Protocol Deviation:** Any change, divergence, or departure from the IRB approved research protocol.

**Non-Compliance:** The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

**Multi-Institutional Guidelines**

The following guidelines are required for all multi-institutional studies in which CCR is serving as the Coordinating Center.

As the Coordinating Center for a trial, it is the Principal Investigator’s (PI’s) responsibility to ascertain that no patients are entered on the trial at a participating institution without full IRB approval. Thus, the NCI IRB must approve the addition of each participating institution to the protocol and will require a copy of the local IRB approval from each participating institution.

The following items must be listed on the protocol title or second page for each participating institution as shown:

- **NAME OF INSTITUTIONAL PI:**
  - INSTITUTION:
  - FWA NUMBER:
  - COMPLETE ADDRESS:
  - PHONE NUMBER:
  - E-MAIL:

- **NAME OF IRB CONTACT:**
  - IRB OF RECORD NAME:
  - COMPLETE ADDRESS OF CONTACT:
  - PHONE NUMBER OF CONTACT:
  - E-MAIL OF CONTACT:

- **NAME OF PHARMACY CONTACT:**
  - COMPLETE ADDRESS OF CONTACT:
  - PHONE NUMBER OF CONTACT:
  - E-MAIL OF CONTACT:

- **NAME OF INSTITUTIONAL STUDY COORDINATOR:**
  - COMPLETE ADDRESS OF CONTACT:
  - PHONE NUMBER OF CONTACT:
  - EMAIL OF CONTACT:

The protocol must use the following format to address each numbered item under section 9.2, *Multi-Institutional Guidelines*. For protocols that do not use the NCI format, the new subsection "Multi-Institutional Guidelines" may alternatively be added as an appendix.

1. **IRB Approvals:** The PI will provide the NCI IRB and the CCR Central Registration Office with a copy of the participating institution’s approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NCI IRB.

2. **Amendments and Consents:** The PI will provide the NCI IRB with copies of all amendments, consents and approvals from each participating institution.

3. **Patient Registration:** All patients from participating institutions must register as patients with the CCR Central Registration Office unless alternative registration procedures are specified in the protocol. The eligibility checklist for the protocol must be sent to the Central Registration Office. 
Office according to standard operating procedures.

4. Data Collection and Toxicity Reporting: The PI will provide specific guidelines for quality assurance, data collection and format, and data receipt by the coordinating institution (recommend at least quarterly). It is recommended that data collection forms be developed for each study. All adverse events from participating institutions must be submitted to the NCI IRB within 10 days.

5. Data and Center Audits: The PI will provide guidelines for audits of participating institutions (recommend at least yearly). Selected patient charts should be audited as well as the participating institutions' Standard Operating Procedures (SOPs) at the time of the visit. Data from participating institutions should be available when the protocol is audited at the NCI.

Women and Minorities in Study Populations

Research benefits and burdens should be distributed fairly. If an individual or group is denied access to a clinical trial that might be beneficial or if some people are singled out to bear the burden of risks associated with a study, the requirement for fairness is not met.

In accordance with NIH policy, the IRB requires researchers to give breakdowns of their subject populations by gender and minority group. Studies with the potential to address issues relevant to both sexes must recruit both genders, and minority populations should be included in a study population wherever feasible. Principal investigators (PIs) must justify the exclusion of women or minorities. The IRB makes exceptions if there is adequate scientific justification for exclusion, such as when a disease predominates in one gender.

FDA guidelines implemented in 1993 give IRBs broad discretion to encourage the entry of women into the early phases of clinical trials. The guidelines now encourage women with childbearing potential to participate in phase I and early phase II trials. FDA believes that early drug trials can be safely conducted on women, even before all animal studies are completed, through sound protocol design. Studies can include pregnancy monitoring, pregnancy testing, and counseling about contraceptives or abstinence. Consent forms should include a statement that there may be unknown risks to the fetus if a woman becomes pregnant while participating in a clinical trial.