IRB Procedures

Application Procedures

Approval to use human subjects must be obtained prior to initiation of the research activity with the subjects. The IRB does not provide retroactive approval for research with human subjects that has been completed or is ongoing.

The NCI IRB has a standard protocol and consent format which must be followed for all CCR protocols. All submissions to the IRB are to be done via iRIS.

The IRB Administrative Office receives all protocols, screens them for completeness, and schedules the protocol for review by the IRB. Incomplete applications, protocols, or informed consent documents will be returned to the investigator and deleted from the IRB agenda until the necessary corrections have been made. Criteria by which review priorities are set:

1. The Principal Investigator (PI) must have all information and forms submitted to the IRB Administrative Office by the meeting deadline, and
2. The protocol must have received Branch review and the submission must include scientific review documentation (review minutes, PI response to review, approval).

Note: All IRB-approved packets are forwarded to the NIH Clinical Center's Office of Protocol Services (OPS) for final processing. New protocols, protocol amendments, and continuing reviews cannot be activated until they are cleared by OPS.

Deputy Ethics Counselor (DEC) Clearance

Avoiding financial and other conflicts of interests is important for NIH, where the trust and protection of research participants is vital to our mission to improve the public health. The number and complexity of laws and regulations in this area makes it difficult to know when there is a problem and what to do. A Guide to Preventing Financial and Non-Financial Conflicts of Interest in Human Subjects Research at NIH (PDF, 3/18/2008) is intended to assist clinical investigators and NIH IRB members in avoiding real or perceived financial and non-financial conflicts of interest. The Clearance of NIH Investigator Personal Financial Holdings by IC Ethics Office (PFH) form is to be used and Guidelines for Completion (PDF, 4/3/2008) are available. The Clearance of NIH Personal Investigator Financial Holdings (i.e., DEC Clearance) is required for the following actions:

- All initial protocol reviews
- All continuing reviews
- Any amendments involving the addition of NIH employee investigators to a protocol, any changes related to the use of commercial products, or any change to an IND/IDE.

Full Board actions do not require a DEC Clearance at the time of submission to the IRB Administrative Office. However, the IRB Administrative Office cannot forward any packet to the NIH Clinical Center’s OPS for final processing without the final clearance. All expedited actions must have the DEC Clearance included in the packet at the time of initial submission to the IRB Administrative Office.

Expedited Review

All protocols/amendments will be submitted to the IRB Administrative Office for final determination regarding expedited review as outlined
below. The IRB Chair/Deputy Chair or a member(s) designated by the Chair/Deputy Chair may review and approve research which involves no more than minimal risk to subjects and in which the only involvement of human subjects is in one or more of the categories listed in the Federal Register notice of Nov. 9, 1998. The IRB Chair/Deputy Chair or other IRB member(s) conducting expedited review may exercise all the authorities of the IRB except that the reviewer(s) may not officially disapprove the research. The reviewer(s) may ask for review by one or more additional IRB members. The reviewer(s) will refer any research protocol to the full Board whenever the reviewer(s) believe that full Board review is warranted. All research approved by expedited review is available for review by each IRB member at the next meeting, and the full committee votes on the actions and this is recorded in the minutes. At this convened IRB meeting, any member may request that an activity which has been approved under the expedited procedure be reviewed by the IRB in accordance with full Board procedures. A vote of the members will be taken concerning the request and the majority will decide the issue. In cases where research activities were initially approved under expedited procedures and subsequently reviewed by non-expedited procedures, the decisions reached at the convened meeting will supersede any decisions made through the expedited review.

Meeting Procedures

IRB meetings are conducted in accord with Roberts Rules of Order. At minimum, the Chair/Deputy Chair conducts the meeting, there is a predetermined agenda, the minutes of the prior meeting are voted upon, and all actions and resolutions require the voice or show-of-hands vote of the members present following discussion and the making and seconding of a motion.

The NCI IRB convenes twice a month (usually on the second and fourth Monday) in a Clinical Center (Building 10) conference room. All meetings are audiotaped to facilitate accurate and thorough meeting minutes. Guests may attend the meetings by invitation only from the Chair/Deputy Chair. Full Board actions require the presence of a quorum of the voting members, defined as a simple majority plus one of the membership including at least one member whose primary concerns are in nonscientific areas. The Chair is counted when determining a quorum and votes.

Approximately 7 days prior to each IRB meeting, members are notified via iRIS that the agenda is final and submissions are available for review. Full copies of protocols being reviewed for responses to stipulations, initial review, amendments, the corresponding consent documents, scientific reviews and other information or correspondence that may be relevant to the protocol approval process is available for review to all members. For continuing reviews the members review a completed NIH form 1195-1, a status memorandum plus current consent document. Documents reviewed through the expedited review process are available in iRIS for review during the meetings. Members receive a cumulative adverse event report describing each event, whether it was expected or unexpected and whether it was described in the informed consent. Each occurrence is discussed by the full board membership.

Principal Investigators (PIs) or their designee are required to be present at the meeting when they have a new protocol under review so that they can respond to questions from IRB members. Each protocol is assigned a primary and secondary reviewer, the selection of which is based on the expertise of the individual IRB members. Ad hoc reviewers may be appointed at the discretion of the Chair/Deputy Chair. In addition, all members of the committee have full review access to IRIS and are expected to be familiar with each protocol and to ask questions and participate in discussions as appropriate. Following the meeting with each PI or their designee, PIs and any Associate Investigators present are excused from the meeting prior to the discussion and vote of the IRB on the protocol. IRB members who are associate investigators on reviewed protocols shall excuse themselves and are also excused from the meeting prior to the vote of the IRB. PIs are not necessarily expected to be present for the continuing review of protocols or amendments, although their presence may be required by the IRB Chair.

Initial Full Board Review

All NCI protocols must be approved by a CCR scientific review committee prior to submission to the IRB or the trial sponsor (e.g., CTEP).

All IRB initial reviews (except those that qualify for expedited review, as described in the above section) and most continuing reviews will be conducted at convened meetings and at timely intervals. A majority of the IRB membership plus one constitutes a quorum and is required to remain present through the entire meeting in order to approve or disapprove a protocol.

An IRB member whose responsibilities are primarily in nonscientific areas must be present at a convened meeting before the IRB can conduct its review of research. The IRB will not have a member participating in initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the Board.

The PI will be notified when his/her protocol will be reviewed by the Committee. For initial reviews it is required that the investigator or his/her designee be present at the IRB meeting to answer any questions.

Initial protocols approved with stipulations and/or recommendations by the NCI IRB must be revised in writing by the PI within 30 days of notification of the IRB’s stipulations or withdrawn from consideration. The response must be submitted via IRIS for approval by the IRB Chair/Deputy Chair or full Board, as outlined in the meeting minutes.

Protocols approved by the IRB (and sponsor, if applicable) are then forwarded to the Clinical Director, NCI and the Director, NIH Clinical Center for final approval through the Office of Protocol Services (OPS). They are entered into the Clinical Center protocols database and a protocol number assigned. The PI will be notified through IRIS of approval when the protocol number has been designated (i.e., 12-C-0101). The final approved version of the informed consent should be available on the Web within 24 hours of final processing by OPS. The IRB Administrative Office will distribute a copy of newly approved protocols to the following:

1. Biostatistics and Data Management Section (BDMS),
2. Central Registration Office,
3. Clinical Center Pharmacy.

Protocols that have Associate Investigators from Institutes other than that of the PI should be forwarded to that Associate Investigator's Clinical
Director for review. Their Clinical Director should indicate by his/her signature on the NIH-1195 or on the title page of the protocol that their Institute can provide the necessary resources.

If the protocol involves the use of an investigational agent, no patient may be treated without the additional approval of the holder of the IND (CTEP or industrial sponsor).

Response to IRB Stipulations/Recommendations

The NCI IRB requires that stipulations be met in writing, using the standard format, before a protocol receives final approval. Either the Chair/Deputy Chair of the IRB, his designee, or the full IRB may certify that the stipulations have been met by the Principal Investigator (PI). In accordance with OHRP guidance, when the convened IRB requests substantive clarifications or changes, IRB approval of the proposed research must be deferred pending subsequent review by the convened IRB of responsive material. Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair/Deputy Chair or other IRB member designated subsequently administratively review the revised research protocol on behalf of the IRB under an expedited procedure. This decision will be documented in the IRB minutes at the time of initial review.

Per the NCI SOP, PIs must respond in writing to IRB stipulations and recommendations from initial reviews within 30 days of receipt of IRB notification, after which time the protocol may be withdrawn from consideration. Under certain circumstances the PI may request an extension not to exceed 6 months.

For continuing review, PIs must respond to the Board's stipulations within 10 days of receipt of IRB notification; failure to do so may result in termination of the study.

Additionally, protocols reviewed and approved by the IRB but not activated (due to lack of CTEP/sponsor approval, drug availability issues, etc.) within one year of IRB approval will also be required to be resubmitted for full committee review.

Protocol Amendments

An expedited review procedure may be used to review and approve minor changes (amendments) that involve no more than minimal risk to the research subject in previously approved research during the period for which approval is authorized.

Any changes in research activities during the period for which IRB approval has already been given may not be initiated by PIs without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subject.

Changes are submitted to the IRB using the amendment form in iRIS. There is no deadline for submission of expedited amendments; they can be submitted and reviewed at any time between IRB meetings.

PIs must respond in writing to IRB stipulations and recommendations within 30 days of receipt of IRB notification. If a PI fails to respond within the allotted time, the protocol will be suspended (closed to accrual). If the PI has not responded within an additional 30 days, the protocol will be permanently closed to accrual, and when all patients are off-study, the protocol will be terminated. Extensions can be granted in extenuating circumstances.

Once the expedited amendment is approved by the IRB Chair/Deputy Chair and NCI Clinical Director, the amendment package is forwarded to the Clinical Center Office of Protocol Services for processing and entry into the CC protocols database. The PI will be notified of approval via iRIS, with the assigned amendment letter (i.e., 12-C-0101A). The IRB Administrative Office will distribute a copy of approved amendments to the following:

1. Biostatistics and Data Management Section (BDMS),
2. Central Registration Office,
3. Clinical Center Pharmacy.

Amendments may not be implemented until formal documentation has been received by the Principal Investigator. Verbal approval will not be given.

IRB Actions

The IRB may vote to approve, approve with stipulations, disapprove, or table a research protocol. These actions, described below, require the vote of a majority of the members present at the meeting. If the vote is not unanimous, the minority opinion is recorded in or attached to the minutes when forwarded for final review and approval. An IRB member may abstain from voting for any reason, without explanation. IRB members who are associate investigators on reviewed protocols shall recuse themselves and are also excused from the meeting prior to the vote of the IRB. A member may change his/her vote until the time the vote is finally announced by the Chair/Deputy Chair. After that, a member's vote may be changed only by permission of the Board which may be given by general consent (see Roberts Rules of Order, Article VIII, Section 46).

1. Approve the protocol (unconditionally).

The IRB accepts the project as presented, finding it meets the requirements as previously outlined. The approval covers both the protocol and the Informed Consent document.

2. Approve the protocol with stipulations.
This action requires that modifications be made to some part of the proposed protocol or that certain information be placed on file with the Board. Modifications or "stipulations" set by the Board may include revising the consent form to explain the procedures or the voluntary nature of participation more clearly, devising mechanisms to maintain confidentiality, using specified safeguards in the procedures, submitting the approval from a collaborating institution, or other changes as deemed necessary. The response to stipulations may be returned to the full Board for review or to the Chair/Deputy or designee when administrative review has been approved by the full Board.

3. **Table the protocol.**

This occurs when the Board feels it has insufficient information to take action, when waiting for full Board review of stipulations to set an approval date, or when the research design contains dangers and should be revised to minimized risk to human subjects.

4. **Disapprove the protocol.**

In this case the Board makes the decision that the potential benefits of the research do not outweigh the risks to the subjects and the research cannot be conducted as written.

**IRB Notifications**

The Board's action is communicated to the PI by iRIS. The investigator is responsible for notification to any sponsor/IND holder, etc. If the IRB disapproves a research protocol, the Board will also provide the reasons for its decision and an opportunity for the investigator to respond.

**Appeal of IRB Actions**

By Federal regulation, and in accord with the NIH Federal Wide Assurance (FWA), institutional officials may not approve research that has not been approved by the IRB. If an investigator believes that his or her proposal has been disapproved because of incorrect, unfair, or improper evaluation by the IRB, he or she may appeal to the IRB Chair, who may then request a reconsideration of the proposal by the Board. An avenue always open to the investigator is to modify the protocol to conform to IRB and HHS/FDA guidelines. However, investigators do not have the option to seek the reversal of an IRB decision by submitting the same protocol to another NIH IRB.

**Protocol Implementation**

A PI may implement a research protocol or changes in an amendment only after an approval from the IRB Chair and ICD Clinical Director has been provided via iRIS. If the protocol involves the use of an investigational agent, IRB approval requires written approval by the holder of the IND (CTEP or industrial sponsor).

**Continuing Review**

Federal regulations require that the IRB provide approval of one year (365 days) or less. The IRB must conduct a minimum of one review of approved research activities every 12 months. The IRB may request an update or periodic review from any investigator at any time. The IRB may, from time to time, conduct such additional reviews as may be necessary to assure that compliance with policies, guidelines, and pertinent law is satisfactory.

If a protocol appears to present unusually great or undefinable risks, the IRB may set the approval interval at less than 12 months. Examples of these studies may include transplant protocols and gene therapy studies. Typically, continuing review for these studies will be required at a maximum of six months. The IRB may consider whether involvement of vulnerable populations merits more frequent review. In addition, if a protocol has a number of protocol-related adverse events which cause concern, or if there are compliance or other problems associated with the protocol, the approval interval may be reduced so that re-review frequency is increased.

Protocol reviews are monitored by the IRB Administrative Office, NCI. iRIS forwards continuing review notices to the Principal Investigator 60 days in advance of the due date, and an overdue notice the day after the due date. If the review has not been completed and turned in to the OPS by the due date, accrual on that protocol is suspended until the review is completed.

The PI must complete and electronically sign the NIH-1195-1. For studies actively accruing patients, the **Active Consent/Assent Document** printed from the Web must be attached. The Branch Chief of the PI should then electronically sign the application.

Most continuing reviews receive full IRB review. After approval by the IRB, the review is forwarded to the OPS, CC; the PI will be notified of final approval via iRIS. The updated consent document should be available on the intranet within 24 hours of the expiration date.

If there are stipulations and/or recommendations, the review will be returned to the PI for revisions. These revisions must be made within 10 days of notification of the IRB stipulations/recommendations via iRIS. The review will then be forwarded to the IRB Chair/Deputy Chair and OPS for final approval.

**Termination**

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the Board's decision, conditions and requirements, or that has been associated with unexpected serious harm to subjects. Serious or continuing noncompliance with the determinations of the IRB may result in the IRB withdrawing approval for a study. Failure to provide a response in a timely manner to notice of annual review is considered cause for suspension or termination of approval.
The NCI IRB also has adopted the policy to terminate a currently approved study that has not accrued subjects within two years of the final approval date. Additionally, studies which have been ongoing for a number of years that have not accrued new subjects may also be terminated at the discretion of the IRB. Studies terminated under these conditions will be required to be re-written according to current guidelines and be submitted for full board review.

Principal investigators may terminate their study by submitting an NIH Form 1195-1 indicating the protocol will be terminated. Note that the entire form must be completed; however, it is not necessary to include a consent form. The PI must contact the Central Registration Office to verify that all patients have been taken off-study. Once verification is received, the termination will be submitted to the IRB Administrative Office via IRIS. It is then forwarded to the OPS, CC, to be recorded. The termination will be reviewed by the IRB members at the next scheduled IRB meeting.

**Note:** For CTEP-monitored studies, a Protocol Status Update form must be completed and sent to CTEP PIO. CTEP will not accept NIH Form 1195-1 as a mechanism to terminate a study.

### Expanded Access Protocol

Expanded access is use of an investigational drug or biologic to treat a patient with a serious disease or condition who does not have comparable or satisfactory alternative therapies to treat the disease or condition. The intent is clearly treatment, not clinical research. There are 3 distinct categories of access: Individual (emergency and non-emergency), intermediate-size and Treatment IND. All but an individual emergency use IND require full board IRB review.

Before beginning this process, please contact your Protocol Support Office or Regulatory Specialist for assistance and to determine the options that are available.

### NCI IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

### Data and Safety Monitoring

PIs must address data and safety monitoring by providing a data and safety monitoring plan in all protocols submitted to the NCI IRB under section entitled Safety Reporting Requirements/Data and Safety Monitoring Plan, found in the CCR Protocol Template.

The NIH policies and guidelines related to data and safety monitoring are as follows:

- NIH Policy for Data and Safety Monitoring *(released June 10, 1998)*
- Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials *(released June 5, 2000)*
- OHSR Information Sheet #18: Guidelines for NIH Intramural Investigators and Institutional Review Boards on Data and Safety Monitoring

These policies apply to investigators in the intramural research program as well as to the extramural investigators.

The IRB must approve the plan and determine what kind of safety monitoring process is required (e.g., PI monitoring only; a single independent monitor: a safety monitoring committee (SMC); or a data and safety monitoring board (DSMB)) based on the level of risk and the number of subjects to be studied. Its determination should be recorded in the IRB minutes. Existing protocols without a data and safety monitoring plan should be amended no later than at the time of IRB continuing review.

A description of these monitoring processes should include a number of elements. Who actually monitors the trial? How often are the data examined in the course of trial conduct? What do the monitors look for? What procedures are in place to insure adequate feedback of information, so that trials involving excessive risk in relation to anticipated benefits are terminated appropriately? What procedures are in place for coordinating multi-center trials, if applicable? The plan should describe the process and oversight in place for assuring that AE reporting requirements are actually met. For multi-center trials coordinated by the intramural NCI, the plan should outline procedures by which the PI establishes a central reporting entity that collects and reports AEs to all necessary destinations, including co-investigators at participating institutions. PIs should describe what quality control procedures are in place assuring data accuracy and completeness. If an IND is in place, quality control procedures are generally stipulated by the IND sponsor and may be simply referenced or summarized in the DSM plan. For studies not done under an IND, the plan should describe whatever procedures are in place to assure data integrity and protocol adherence.

### Data Safety Monitoring Board (DSMB)

A DSMB is an impartial group established to oversee a clinical trial and review the results to determine if they are acceptable. Members of a DSMB must be multidisciplinary and include members with relevant clinical and statistical expertise. The DSMB should meet at least annually or more often depending on the activity and nature of the clinical trial being monitored.

Protocols that **WILL REQUIRE** a DSMB include:

- Protocols that generate blinded, randomized data;
- Any phase III single institution trial (NCI only) presenting more than minimal risk;
- Phase III multi-institutional protocols coordinated by the CCR presenting more than minimal risk without an outside DSMB.

Protocols that **MAY REQUIRE** a DSMB include:
• Protocols that the NCI IRB believes require special scrutiny because of high public interest, public perception of risk, or the inclusion of vulnerable populations.

Safety Monitoring Committee (SMC)

The CCR's general SMC is charged with advising the Clinical Director, CCR, the NCI IRB, and other senior leaders at the NCI CCR as appropriate on the safety and continuing scientific validity of clinical protocols being conducted by NCI CCR investigators.

The SMC’s responsibilities include the review of patient safety data (specifically toxicities and the risk:benefit ratio of the trial); interim analyses to determine if the primary objectives will be accomplished (including patient accrual, adherence to the study design, and outcome measures); and the release of protocol-related primary outcome data.

• All NCI CCR multi-institutional treatment protocols for which the NCI CCR is the coordinating site, unless the study has already a designated Data and Safety Monitoring Board (DSMB) or equivalent. These studies will be monitored across the sites for unusual, significant toxicities that are related to the investigational agents being used. The SMC will not monitor a CTEP-sponsored protocol of this type if this is the only SMC qualifying criteria for the protocol.
• All protocols using gene transfer or gene therapy methodology. Monitoring of these protocols will focus on unusual toxicities specific to gene therapy.
• All protocols that the CCR believes require special attention due to high public interest or public perception of risk or potential conflict of interest. These include studies where the PI or an AI holds a patent on any agent being used in the protocol. For these protocols, the review will focus on unusual, significant toxicities that are related to the investigational agents being used, as well as on the potential perception of a conflict of interest regarding issues such as the continuing study relevance vs. PI benefit.
• All protocols that are deemed to pose potentially very high risk to patients.

Protocols can be referred to the SMC by the Clinical Director, the Branch Chief of the branch in which the protocol originates, or the IRB Chair.

Timing of protocol review by the SMC:

Protocols referred to the SMC will be reviewed initially as soon as possible after their annual NCI-IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC.

For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period.

This protocol will require oversight from the Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual NCI-IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

Note: Please contact Susan McMullen or 301-402-5931 if your protocol requires SMC review or if you have any questions about the above criteria.

Consultation with Principal Investigators

Investigators may call upon the IRB Chair/Deputy Chair/IRB Coordinator or other members for consultation regarding the protection of human subjects. Any consultation is informational in nature; it is neither interpretative nor a final decision.

Outside Review of Protocols

When it is determined that consultants or experts will be required to advise the IRB in its review of a protocol, the research protocol will also be distributed to the consultant or expert.

IRB Minutes and Records

The minutes of IRB meetings will 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, including the reasons for any opposing vote (see above); the basis for requiring changes in or disapproving research; and a written summary of the discussion of controversial issues and their resolution.

The IRB maintains protocols and consent documents that it has reviewed including continuing reviews; minutes of the meetings; a current approved membership list; progress reports submitted by investigators; reports of injuries to subjects; all correspondence between the IRB and investigators; statements of significant new findings provided to subjects; and documentation of collaborative and cooperative research activities occurring at other institutions with FWAs, including documentation of protocol and consent form approval by the IRBs at these sites. Records and documents are retained for least three (3) years after completion of the research.