

DEPARTMENT: Yale University Human Investigation Committee  
POLICY NUMBER: XX.AA  
SECTION: Centralized Institutional Review Boards  
REVIEW RESPONSIBILITY: IRB Policy and Procedure Committee, Yale Cancer Center, General Clinical Research Center  
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## **Yale University School of Medicine HIC Policy Regarding: Use of the National Cancer Institute's Central IRB (CIRB)**

### **Purpose:**

The purpose of this policy is to describe when Yale University will authorize the review and approval of research protocols by the National Cancer Institute's (NCI) Adult and Pediatric Central Institutional Review Board (CIRB) to substitute for the review and approval conducted by one of Yale's Institutional Review Boards (IRB).

### **Background:**

The CIRB initiative is a project sponsored by the NCI, in consultation with the Office of Human Research Protections (OHRP). The CIRB features a "facilitated review" process that can streamline local IRB review for national multi-center cancer treatment trials.

When permitted, and as per this policy, Yale may authorize the CIRB to serve as its IRB of record and thus serve as the primary IRB responsible for the review and approval of research protocols. In these instances, the local IRB, the Human Investigation Committee, or HIC, retains local context and oversight responsibilities.

The Adult CIRB commenced reviewing protocols in January 2001. The Pediatric CIRB began meeting in November 2004.

### **Policy:**

The HIC is responsible for determining when Yale University may authorize the CIRB approval of a research protocol to substitute for the review and approval of the protocol by the HIC.

Investigators may request, and the HIC may authorize the acceptance of the CIRB approval for Phase III adult clinical trials submitted to the CIRB for review from the following cooperative oncology groups: ACOSOG, CALGB, ECOG, GOG, NCCTG, NCIC, NSABP, RTOG, and SWOG, as well as any other Phase III protocols opened in the Cancer Trials Support Unit (CTSU).

The HIC may also authorize the Pediatric CIRB to serve as its IRB of record and thus accept the Pediatric CIRB approval of all NCI-approved COG Phase 2, 3, and pilot trials.

Investigators requesting that the HIC authorize the CIRB approval of a protocol are required to use the protocol proposal and review process required by the Yale Cancer Center. Additionally, protocols utilizing the General Clinical Research Center must be reviewed and approved by the General Advisory Committee prior to requesting authorization of CIRB approval from the HIC. Please refer to the Clinical Trials Office for assistance.

## **Procedures and Responsibilities:**

### **Responsibilities of the Principal Investigator**

#### ***1. Preparing the Application***

A Yale principal investigator (PI) is notified of the availability of a new protocol through activation announcements from the Cooperative Groups. The PI, or designated staff, check the CIRB website to see if the study is CIRB-Approved.

Investigators, who wish to enroll subjects in a CIRB-approved protocol must download all CIRB documentation from the Members Area of the CIRB website. Required documents include,

- the CIRB application,
- the protocol,
- informed consent documents,
- notification letters,
- any serious adverse event reports and amendments,

The HIC will download the primary reviews and minutes as they are only available to the IRB.

Other documents that must be submitted with the application include:

- the HIPAA Research Authorization form(s) and/or Waiver(s),
- recruitment materials,
- notices of approval from other Yale protocol review committees, and
- the Yale University Protocol-Related Conflict of Interest form, when appropriate.

The informed consent document must include the CIRB approved contents and be formatted in the Yale School of Medicine format. Formatting in this instance refers to the appropriate “Yale University – Yale New Haven Hospital” heading (and other site locations as appropriate), name of the Yale Principal Investigator and sponsor information. The consent document must include the version date, approval date and the expiration date that are noted on the CIRB document. Text written as instruction to investigators for completing the forms or attaching documents should be removed from the consent document.

## Reviews By Other Committees

Yale University policies require that the following internal committees review protocols. Thus documentation of approval from the following committees must be included in the protocol submission packet sent by the investigator to the HIC for facilitated review.

- **YCC Office of Protocol Review and Monitoring:** All protocols must be processed through the Office of Protocol Review and Monitoring prior to submission to any oversight committee.
- **Protocol Review Committee (PRC):** Reviews all research conducted by Yale University faculty that involves the use of the Yale Cancer Center. Reviews include new applications, requests for continuing approval or renewals and major amendments.
- **YNHH Radiation Safety Committee:** Reviews all research involving human subjects at YNHH and which also involves the use of radioactive materials that are approved by the FDA and used on or off label.
- **Gene Transfer Subcommittee of the Institutional Biosafety Committee** Reviews all research involving human gene transfer products under the purview of the Recombinant DNA Advisory Committee (RAC)
- **YNHH Radioactive Drug Research Committee:** Oversees the use of radioactive materials which require no IND nor FDA approval and which are prepared at the Yale Medical Center.
- **General Advisory Committee (GAC):** Reviews all research conducted by the Yale University faculty that utilizes the General Clinical Research Center resources located at Yale New Haven Hospital.
- **Magnetic Resonance Review Committee:** Reviews all research utilizing MR resources at The Anlyan Center (TAC). Implementation date pending. Please check the HIC website for updates.

## CIRB Responsibilities:

The CIRB receives the protocol, the informed consent document(s) and an appropriate investigator drug brochure from the Cooperative Group via the Protocol Information Office at NCI.

The documents are reviewed at a convened CIRB meeting, which occur monthly. The Board takes one of the following actions for each protocol: approve, approve pending modification, table, or disapprove. The Study Chair and the Cooperative Group sponsor are notified after an approval or disapproval.

Primary reviews, minutes, notification letters, and any other correspondence generated by the CIRB are posted in a separate section of the CIRB web site for participating institutions to access. See <http://www.ncicirb.org/> for list of protocols, participating sites and other information.

The CIRB also conducts continuing reviews and reviews of serious adverse events (SAEs), Data Safety Monitoring Board (DSMB) reports, protocol amendments, recruiting materials for national recruitment initiative, etc... The CIRB findings on these actions are

posted on the CIRB web site for prompt access by participating investigators and institutions.

The CIRB distributes protocol activity updates to Local investigators and IRBs to notify participating institutions of status changes in protocols and other information relating to protocols such as, activation and closure of CIRB protocols and drug notices and safety reports. These updates are provided on a periodic basis. For more information see [http://www.ncicirb.org/CIRB\\_ActivityUpdates.asp](http://www.ncicirb.org/CIRB_ActivityUpdates.asp) .

## **Responsibilities of the HIC:**

### ***1. Review of the Protocol and Approval Documents***

The HIC is required to conduct a "facilitated review" of the study that the investigator wishes to conduct at the University. This "facilitated review" is conducted by a HIC Chairperson or a designated voting member of the HIC or a designated subcommittee of the HIC. The role of the HIC reviewer(s) is to determine whether there are local concerns that need to be addressed and whether to accept the CIRB review and approval. The HIC must comply with OHRP guidance that, "...an institution relying upon another institution's IRB has a responsibility to ensure that the particular characteristics of its local research context are considered through subsequent review by appropriate designated institutional officials, such as the Chairperson and/or other members of its local IRB."

The designated reviewer(s) examines the materials made available by the CIRB. These documents include CIRB minutes that reflect the discussions of the protocol, approved informed consent documents and other information. The designated person(s) determines whether the CIRB review and approved informed consent documents are acceptable and whether they are appropriate in their local context.

The HIC has the authority to propose/approve additions to the protocol or word substitutions in the informed consent (see following paragraph). The HIC also has the option to accept the CIRB approval "as is" or accept it with minor revisions (see below). The HIC may also decide not to accept the CIRB review and require that the investigator submit the protocol for full HIC review. If the designated reviewer(s) does not accept the CIRB review, the CIRB written materials may still be utilized as resources for the HIC review process.

During the facilitated review, the HIC may add stipulations or local requirements to protocols. These stipulations will be added to increase subjects' safety, to clarify procedures or when otherwise deemed appropriate. These stipulations, however, will not delete or contradict any protocol contents. Additions or deletions to the informed consent regarding state and local law, institutional requirements, or Yale and HIC policies, may also be considered. The HIC may make minor word substitutions or additions in the informed consent document to facilitate better comprehension by the local population.

The proposed changes may not however, alter the meaning of the CIRB approved contents.

## ***2. HIC Acceptance of the CIRB-Approved Protocol***

The HIC must notify the CIRB Administrative Office each time it accepts the CIRB review of a protocol. This process is completed through the CIRB website. A separate form must be submitted for each protocol review that is accepted. The CIRB will respond back to the HIC and the investigator, via email, acknowledging the review. This acknowledgement is required prior to the HIC releasing a stamped consent document to the Yale Principal Investigator.

The HIC will not review nor accept CIRB approval of a study if the enrollment of the study has been suspended by the CIRB or by the oncology group.

The CIRB will notify the HIC and the investigator when there are any actions taken on the protocol, e.g., an SAE report provoking a change in the consent form, an approved protocol amendment, a change in the protocol/informed consent resulting from the Continuing Review, etc..

The HIC will retain reviewer findings on each initial submission. The findings will serve as documentation and justification of requested informed consent changes. The documentation will also serve as justification that the proposed study is considered appropriate to be conducted at Yale University.

The HIC will notify CIRB of any outstanding issues noted during reviews.

The investigator must send a copy of the Yale version of the CIRB approved consent form and appropriate HIC acknowledgement documentation to the Cooperative Group administering the protocol.

## ***3. Post HIC Acceptance of CIRB Approval***

Once a new application has been approved by the HIC and acknowledged by the CIRB, the CIRB is responsible for reviewing and notifying Yale investigators and IRB staff of any changes, amendments, or modifications approved by the CIRB. The PI is responsible for ensuring that the CIRB acknowledgement is received prior to the study being initiated at Yale. The Yale PI is also responsible for insuring that only updated and valid consent forms that have the acknowledgement stamp by the HIC are used to enroll subjects into Yale protocols PI. All approved documents and consent forms must be retained by the PI and/or their appointed study coordinators pursuant to good clinical practice and confidentiality and security standards.

#### ***4. HIC Oversight***

The HIC will assume the oversight responsibility and perform IRB functions in compliance with federal regulations. These responsibilities include, but are not limited to, reviewing potential protocol-related conflicts of interest, insuring that all Yale researchers and staff are appropriately qualified to conduct the protocol, monitoring and/or auditing protocol records and the consent process to insure compliance with the protocol, insuring that the protocol is conducted in accordance with federal and university regulations and policies, and reporting any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance to federal department agencies as required.

The HIC will retain a comprehensive protocol file for all studies approved by the CIRB. A copy of all correspondence from CIRB regarding each individual protocol will be retained at the HIC office. Copies of facilitated review findings by the HIC Chairperson or his/her designee will also be maintained in the HIC file.

Upon receipt of the continuing review approval by CIRB, the HIC will conduct an administrative review of the protocol to insure that the study is progressing in a manner that is consistent with the original submission and Yale standards. Records of this administrative review will also be retained in the protocol file.

CIRB will also notify the HIC of any termination or suspension of a study. Yale will notify the CIRB and the appropriate federal oversight agencies of instances of serious or continuing noncompliance with the federal regulations.

### **Other Protocol Related Actions and Considerations**

#### ***1. Transferred Active Studies/Re-Review***

The principal investigator, the HIC, the sponsoring Cooperative Groups and the CIRB will collaborate regarding whether the IRB approval of protocols currently active at Yale can be transferred from the HIC to the CIRB. In all instances, the decision to transfer IRB approval authority will be made so as to insure the welfare of human subjects engaged in research at Yale University.

Transferring IRB approval from the HIC to the CIRB can occur when the following conditions are met:

- The study is listed as approved on the CIRB website.
- The Yale investigator has submitted the appropriate termination paperwork to the HIC to “close out” the Yale protocol. The investigator must note in a cover letter that he/she wishes to transfer IRB review responsibilities to the CIRB.

- The HIC reviewer has submitted the appropriate documentation to the CIRB requesting that the CIRB serve as Yale's designated IRB in review of the protocol.
- The CIRB has accepted the HIC request to serve as Yale's IRB for the specific protocol.

## ***2. Continuing Review Submissions***

The approval duration and anniversary date for an individual protocol is based on the date that the protocol was **reviewed by the CIRB** and not the date that the HIC accepted the CIRB approval. The CIRB will conduct the required subsequent review in such a manner so as to insure continued approval of the study.

Yale investigators and/or their appointed study coordinators/correspondents and IRB reviewers and staff will be provided with an electronic notice of continuing review by the CIRB.

Once the CIRB has issued a notification of continuing review or, reapproval, the PI must submit to the HIC the newly approved informed consent document in Yale format. The HIC will return to the Principal Investigator a notice that it has accepted the CIRB reapproval. The informed consent document will be stamped and sent back to the Principal Investigator. The HIC is responsible for notifying the CIRB that it has accepted the reapproval conducted by the CIRB.

Investigators cannot enroll subjects, conduct research activities nor collect research data if the IRB approval of a protocol has expired. If the Yale investigator believes that the health or welfare of a subject will be jeopardized if a study treatment is discontinued, the investigator may submit a written request to the HIC with justification for continued treatment with currently enrolled subjects. HIC approval of this request is required.

## ***3. Amendments***

Yale investigators and their appointed study coordinators/correspondents and IRB reviewers and staff will be provided with an electronic notice of any changes, amendments, or modifications to protocols approved by the CIRB and accepted by the HIC.

Once the CIRB has issued a notification of the approval of an amendment that affects the informed consent document, the PI must submit to the HIC the CIRB amendment request, the PRC amendment request (if necessary), the CIRB amendment approval letter, the updated protocol (if appropriate) and any newly modified informed consent documents in Yale format. An acceptance letter will be sent to the Principal Investigator along with the stamped and validated informed consent document(s).

Major changes to the protocol, referred to as major amendments, are those that affect the protocol design and/or the risk/benefit ratio. These must be reviewed by the PRC prior to the amendment being implemented at Yale.

#### ***4. Protocol Deviation Reporting***

Yale Principal Investigators are required to report major protocol deviations and violations to the HIC and as required by the sponsoring Cooperative Group. The HIC's Protocol Deviation Report Form can be found at <http://info.med.yale.edu/hic/forms/index.html> .

#### ***5. Adverse Event Reports and Unanticipated Problems***

Adverse Event reports should be forwarded as required by the Cooperative Groups. A serious or unanticipated adverse event that is possibly, probably or definitely related to the subject's participation in research which occurs at Yale University must also be reported to the HIC within 48 hours of it becoming known to the Yale investigator.