

**PARTNERS HUMAN RESEARCH COMMITTEE  
POLICIES AND PROCEDURES**

**Initial and Continuing Review of Human-Subjects Research and Proposed Changes in  
Approved Research at a Convened PHRC Meeting**

1.0 PURPOSE

The purpose of this policy is to define the procedures the Partners Human Research Committees (PHRC) follow when conducting initial and continuing review of human-subjects research and clinical investigations and review of proposed changes in approved research at a convened meeting of the PHRC.

This policy is established to comply in part with the regulatory requirement in 45 CFR 46.103(b)(4)(i) and 21 CFR 56.108(a)(1) requiring IRBs to have “written procedures which the IRB will follow for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution.”

2.0 SCOPE

Non-exempt human-subjects research and clinical investigations reviewed by the PHRC at a convened meeting are subject to this policy.

3.0 DEFINITIONS

As used in this document, human-subjects research encompasses activities that meet the DHHS definitions of *research* and *human subject* and/or the FDA definitions of *clinical investigation* and *human subject*. The DHHS definition for *research* and *human subject* and the FDA definition for *clinical investigation* and *human subject* are provided below.

*Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. [45 CFR 46.102(d)]

*Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information. *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect

that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. [45 CFR 46.102(f)(1)(2)]

*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 studies. The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous... [21 CFR 50.3(c) and 21 CFR 56.102(c)]

*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. [21 CFR 50.3(g) and 21 CFR 56.102(g)]

*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. [45 CFR 46.102(i)][21 CFR 56.102(i)]

#### 4.0 POLICY

The PHRC must review all non-exempt human-subjects research and clinical investigations at a convened meeting at which more than half the members, including at least one physician-scientist member and one nonscientist member, are present unless the research is eligible for review using the expedited review procedure. When reviewing non-exempt human-subjects research and clinical investigations, the PHRC Chairpersons and PHRC members are subject to the *Partners Conflicts of Interest Policy for IRB Members*.

#### 5.0 PROCEDURES

##### 5.1 Meeting Dates

The PHRC meeting dates and times are determined by the end of each year for the following year. Members are informed of the meeting schedule prior to the end of the year in order to reserve the dates and times on their calendar. The meeting dates are posted on the PHRC website.

## 5.2 Quorum

Human-subjects research and clinical investigations that cannot be reviewed using the expedited review procedure are reviewed at a convened meeting of a quorum of the membership of the PHRC, including at least one physician-scientist and at least one member whose primary concerns are in nonscientific areas. A *quorum* is defined as more than one-half the voting membership.

## 5.3 Determining Attendance and Assigning Reviewers

5.3.1 Prior to each convened meeting, members are asked if they will attend the meeting. This is necessary to determine whether the requirement for quorum is met and that members with the appropriate scientific or scholarly expertise will be in attendance.

5.3.2 The presiding PHRC Chairperson or Administrative Chairperson reviews the agenda and list of members expected to attend and assigns reviewers to each protocol. Generally, protocols are scheduled for review by receipt date; however, the PHRC reserves the right to reschedule protocols for review based on the experience and expertise of the members planning to attend the PHRC meeting.

5.3.3 The presiding PHRC Chairperson or Administrative Chairperson is responsible for ensuring that at least one member attending the meeting has the necessary knowledge and expertise to review each of the protocols listed on the agenda.

5.3.4 When the agenda includes protocols that involve vulnerable populations, the presiding PHRC Chairperson or Administrative Chairperson is responsible for ensuring that at least one member attending the meeting has knowledge of and/or experience in working with the study population.

5.3.5 When making reviewer assignments, the presiding PHRC Chairperson or Administrative Chairperson takes into consideration the scientific discipline, the study population, and study procedures described in the protocol and the experience and expertise of the members attending the meeting.

5.3.6 The qualifications, experience, and expertise, as well as representative capacity of each member, are documented in the PHRC roster. Member

CVs are also on file in the Human Research Office. The presiding PHRC Chairperson or Administrative Chairperson has access to the PHRC roster and member CVs when making reviewer assignments.

- 5.3.7 The primary reviewer is typically a physician-scientist or other scientist with experience in working with the population being studied and/or expertise in the type of research under consideration, although this is not an absolute requirement, depending upon the type of study.
- 5.3.8 The secondary reviewer is typically an individual who can provide another perspective, for example, a layperson, genetic counselor, nurse or parent. The secondary reviewer, therefore, complements the scientific or scholarly expertise of the primary reviewer.
- 5.3.9 Both the primary and secondary reviewers are responsible for performing an indepth review of all aspects of the protocol, consent form and associated materials, including when applicable, the application for funding (e.g., NIH grant application).
- 5.3.10 The primary and secondary reviewers are provided with a reviewer worksheet and points to consider for guidance when reviewing the research.
- 5.3.11 Reviewers are encouraged, although not required, to contact the principal investigator prior to the meeting if they have questions about the study, particularly if they have significant concerns about the study or believe additional information is needed for the PHRC to be able to assess the risks and anticipated benefits, if any, to subjects and the importance of the knowledge that may be expected to result from the research.

#### 5.4 Use of Consultants

- 5.4.1 Although rarely needed because of the depth and breadth of the membership of the PHRC, consultants may be used to supplement or provide expertise not available on the PHRC. When the presiding PHRC Chairperson or Administrative Chairperson reviews the draft agenda to make primary and secondary reviewer assignments, s/he is responsible for determining whether the PHRC membership includes the necessary expertise to review the protocol.
- 5.4.2 When, in the opinion of the presiding PHRC Chairperson or Administrative Chairperson, the PHRC membership lacks the expertise needed to review the protocol, the presiding PHRC Chairperson or Administrative Chairperson, in consultation with the Director and Chair of the PHRC or designee, identifies potential expert consultants.

- 5.4.3 Additionally, the PHRC may vote to defer action on a protocol and may require an expert in the scientific area or discipline to review the research and provide consultation to the PHRC. Potential consultants will be identified and agreed upon by the PHRC, or as indicated above.
- 5.4.4 Consultants are subject to the *Partners Conflicts of Interest Policy for IRB Members* and must confirm in writing that they have no conflict of interest. If the consultant agrees to review the research and the consultant has no conflict of interest, s/he is provided with all of the forms and documents submitted to the PHRC for review.
- 5.4.5 Consultants are asked to attend the meeting to present their findings relative to the scientific merits of the study, the risks and potential benefits to subjects, and alternative treatments or procedures, and to answer questions; however, if the consultant is unavailable to attend the meeting, s/he may provide written comments for distribution or communication to the PHRC members. Consultants are not voting members, and their attendance is recorded in the Minutes as guests (consultant).

## 5.5 Distribution of Materials and Review by Members

Investigators who rely upon the PHRC for IRB review of human-subjects research and clinical investigations are required to complete application forms and provide all required information and documents to the Partners Human Research Office for review by the PHRC as described in the *Protocol Submission Instructions*, the *Continuing Review Submission Instructions*, and applicable forms.

Approximately one week prior to the meeting, copies of forms and documents submitted for PHRC review for each item on the agenda are distributed to all members planning to attend the meeting. All members are provided with guidance documents that include the regulatory criteria for approval and requirements for informed consent. For initial review and proposed changes, the agenda also includes references to relevant regulatory documents and PHRC policies and procedures.

Reviewers are provided with a reviewer worksheet to prepare their review. Assigned reviewers are responsible for an indepth review of all of the materials provided to them relevant to the research including, when applicable, the funding application. Members who are not assigned to review the protocol are expected to review all of the materials provided to them relevant to the research in sufficient depth to vote on the research at the convened meeting.

### 5.5.1 Initial Review

5.5.1.1 For initial review, all members attending the meeting receive a copy of the required forms, protocol summary, recruitment materials, detailed protocol, and consent form submitted by the investigator.

5.5.1.2 In addition, the primary and secondary reviewers and the PHRC Chairpersons receive copies of the drug/device brochure, the application for funding (e.g., NIH grant), and standardized instruments with which the PHRC members are familiar (e.g., SCID, Ham-D). These documents are available to all members upon request.

#### 5.5.2 Continuing Review

5.5.2.1 For continuing review, every member attending the meeting receives copies of the required forms and documents submitted by the investigator for continuing review (see *Continuing Review Submission Instructions and Checklist*).

5.5.2.2 All members also receive a summary report for each protocol that provides an overview of the protocol, a list of study personnel, and list of all PHRC reviews. The entire protocol file and minutes of meetings at which the protocol was reviewed previously are available to all members upon request.

#### 5.5.3 Proposed Changes

5.5.3.1 For review of proposed changes to approved research, every member attending the meeting receives copies of the required forms and documents submitted by the investigator for the proposed change.

5.5.3.2 At a minimum, all members receive a copy of the amendment form, and forms and revised documents incorporating the proposed changes.

5.5.3.3 The entire protocol file is available to all members upon request.

#### 5.6 Conflicts of Interest

5.6.1 PHRC members are subject to the *Partners Conflicts of Interest Policy for IRB Members*. The agenda for every meeting includes a reminder about the conflicts of interest policy.

5.6.2 Any member with a conflict of interest is asked to recuse him/herself and leave the room while the protocol is being reviewed, except to provide

information to the PHRC, after which the member must leave the room for the discussion and vote on the protocol.

5.6.3 The names of those voting members who were recused from voting due to a conflict of interest are recorded in the Minutes.

5.6.4 Recused members are not counted towards the quorum requirement; therefore, if a quorum of the membership is not present for the review of any protocol, no vote is taken and the protocol is held over for review at the next meeting of the same PHRC panel.

## 5.7 Discussion and Vote

5.7.1 The PHRC administrator takes attendance at the meeting and records voting members present and absent for each review. Late arrivals, early departures, and individuals recused or out of the room for one reason or another during the discussion and vote on each protocol are recorded in the Minutes.

5.7.2 The presiding PHRC Chairperson and assigned reviewers lead the discussion of each new protocol, continuing review, or amendment listed on the meeting agenda.

5.7.3 The primary reviewer presents a brief synopsis of the research protocol, with the expectation that the other members have reviewed the protocol materials. The primary reviewer is responsible for covering the scientific background and rationale, study design, how the research differs from and compares to standard care, appropriateness of the study population and the inclusion/exclusion criteria, the risks and potential benefits to subjects, alternative treatments or procedures, as well as the criteria for IRB approval and, when applicable, additional protections for pregnant women, human fetuses, and neonates, children, and individuals with impaired decision-making capacity.

5.7.4 Primary reviewers may have particular insight into referral patterns, clinical standards within the community, or routine care for the conditions under study, and it is expected that these are also part of the presentation to the PHRC.

5.7.5 Secondary reviewers are asked to present any additional clarifications or commentary on the study plan, and any questions or concerns, or modifications s/he would require for approval.

5.7.6 Both the primary and secondary reviewers are expected to provide an indepth review of the consent form and identify missing required elements and when, applicable, additional elements for informed consent.

Additionally, reviewers may comment on the reading level and style of the consent form and provide detailed suggestions for improvement. Consent form comments may be handwritten on the form, or provided in written commentary as part of the review.

- 5.7.7 Reviewers are encouraged to provide written comments so that the PHRC Chairpersons can convey the questions and concerns raised by the reviewers and the PHRC, and/or specific modifications required by them accurately and precisely.
- 5.7.8 After the primary and secondary reviewers have presented the study and their review comments, the presiding PHRC Chairperson opens the protocol up for discussion by the membership. The PHRC Chairperson and members may direct specific questions to the assigned reviewers or to other members with specific expertise or viewpoints (e.g., a layperson, nurse or other member who may bring a different perspective to the discussion).
- 5.7.9 At the end of the discussion, one of the reviewers or another member makes a motion to approve, require modifications in the research (to secure approval), defer action on (pending receipt of additional information), or disapprove the protocol. A vote on the motion is taken (for, against, or abstain) and recorded in the Minutes. All motions are decided by majority vote of the members present for the review. A quorum of the members of the PHRC (more than one-half the members) must be present in order for the PHRC to take a vote.

## 5.8 Determining Frequency of Continuing Review

- 5.8.1 When the motion is to approve or require modifications in (to secure approval), the motion includes the duration of PHRC approval. When determining the duration of approval, the PHRC considers the degree of risk to subjects. The duration of approval may not exceed one year from the date at which the protocol was approved (or approved with modifications) at a convened meeting of the PHRC.
- 5.8.2 When the risks to subjects related to participation in the research are greater than the risk associated with alternative treatments or procedures, if any, the PHRC will consider requiring that continuing review be conducted in less than one year, or one year with case-by-case reporting. Examples of protocols that may be considered for review more frequently than annually include:
  - phase I studies of a challenging or novel new drug or biologic;
  - studies involving Category A significant risk devices;

- studies in which healthy volunteers may undergo anesthesia or medical procedures involving sedation with no direct health benefits;
- studies for which there is little external oversight or data safety monitoring;
- studies involving gene transfer or xenotransplantation; or
- studies involving infectious agents.

5.8.3 The approval period begins the date the protocol is approved (or approved with modifications) at the convened meeting and expires as of the expiration date.

5.8.4 Continuing review of the research is required until the research has been completed or has been closed prior to completion. The investigator must submit the continuing review form to document that the study has been completed or is being closed prior to completion. For multi-site research, the research may be considered completed or may be closed prior to completion when the investigator at this site is no longer collecting, receiving, or analyzing identifiable data.

5.8.4.1 Continuing review of research previously approved by the convened PHRC may be conducted using the expedited review procedure as follows:

(a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

(b) where no subjects have been enrolled and no additional risks have been identified; or

(c) where the remaining research activities are limited to data analysis.

5.8.4.2 Additionally, continuing review of research previously approved by the convened PHRC may be conducted using the expedited review procedure where the research is not conducted under an investigational new drug application (IND) or investigational device exemptions (IDE) where categories two (2) through eight (8) do not apply but the PHRC determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified since the last review.

## 5.9 Determining Which Studies Need Verification from Sources Other Than the Investigators

Investigators are required to provide the PHRC with all relevant information regarding the conduct of the research and fulfill all requirements for prompt reporting to the PHRC of unanticipated problems involving risks to subjects or others.

5.9.1 In order to ensure that the research is conducted in compliance with all applicable regulations for the protection of human subjects, the PHRC may require verification of information from sources other than the investigator. Such independent verification may be considered in the following situations:

- complex projects involving unusual levels or types of risk to subjects;
- studies being conducted by persons who have previously failed to comply with all regulations or requirements of the PHRC;
- study performance that is questioned at the time of continuing review; or
- studies in which substantial segments of the project are conducted off site by collaborators, or in which Partners investigators conduct research off site.

5.9.2 Independent verification may include, but is not limited to:

- audit by the Human Research Quality Improvement Program;
- communications between the FDA and the sponsor (IND/IDE holder);
- communications from any monitoring group, e.g., DSMB or DMC
- GCRC evaluations and reviews;
- NIH communications and reviews; and/or
- communications with IRBs at collaborating sites.

## 5.10 Requiring Modifications or Deferring Action and Responses to Review Notification Letters

### 5.10.1 Require modifications in research to secure approval

When the PHRC votes to require modifications in the research (to secure approval), the Principal Investigator (PI) is notified in writing of the action voted on by the PHRC and the required modifications to the research. The PI is asked to submit a point-by-point response and revised documents to the PHRC within 60 days of the review date. Unless the PI requests an extension or there are extenuating circumstances, the protocol is withdrawn from further review at the end of the 60-day period if no response is received.

When received, the presiding PHRC Chairperson or Administrative Chairperson reviews the PI's response, including revised documents, and documents on the review form and checklist whether the modifications required by the PHRC have been made and whether the protocol can now be fully approved. If the modifications have not been made as required, the response is scheduled for review at the next convened meeting of the reviewing PHRC.

Proposed changes submitted with the response are reviewed in accordance with the policies and procedures for review of proposed changes, i.e., either at a convened meeting or, if minor, using the expedited review procedure.

#### 5.10.2 Defer research for more information

When the PHRC votes to defer action pending receipt of additional information, the PI is notified in writing of the action voted on by the PHRC and any questions and concerns that need to be addressed as well as modifications required to the research. The PI is asked to submit a point-by-point response and revised documents to the IRB within 60 days of the review date. Unless the PI requests an extension or there are extenuating circumstances, the protocol is withdrawn from further review at the end of the 60-day period if no response is received.

When received, the PI's response, including revised documents, is scheduled for review at the next convened meeting of the reviewing PHRC.

#### 5.11 Disapprove

When the PHRC disapproves the research, the PI is notified in writing of the action voted on by the PHRC and the basis for the disapproval. Disapproval means that the study as designed cannot be approved and the PHRC can think of no modifications or additional information that will likely result in an approval.

The decision of the PHRC to disapprove the research cannot be overruled by any other institutional body or individual(s); however, an investigator may appeal the decision of the PHRC in writing directly to the Director and Chair of the PHRC. The Director and Chair of the PHRC is responsible for reviewing the appeal with the presiding PHRC Chairperson. The appeal is then scheduled for review at a convened meeting of the PHRC that disapproved the research. The investigator may appeal the decision of the PHRC in person at the convened meeting.

#### 5.12 Notification of Principal Investigator and the Institution

- 5.12.1 Principal Investigators are notified in writing of PHRC approval of initial and continuing review of human-subjects research and clinical investigations. The approval letter includes the date of PHRC approval and the date upon which PHRC approval expires.
  
- 5.12.2 Minutes of PHRC meetings are made available electronically to the Institutional Officials in a shared file area. In addition, the Human Research Office provides individuals and/or departments within Partners with responsibility for some aspect of the human research protection program electronic access to PHRC review information via the Insight Research Portal.