Chapter 8
Process of IRB Submissions

This chapter focuses on the IRB submission and review processes. It includes an overview of iStar, the electronic application system used to submit all human subjects proposals to the IRB, the criteria for IRB approval, the review process for the different submission types, and IRB determinations and correspondence details.

8.1 IRB Online Application (iStar)

The IRB Submission Tracking and Review (iStar) online system supports all applications: new study, continuing review, amendment, and reportable event (for safety and other reports). Access to the iStar system is granted to the research team and IRB staff depending on roles and oversight responsibilities.

The application guides users to questions specific to the nature of their research, and ensures that information required for regulatory purposes is appropriately collected. For example, if a protocol includes minor subjects, users are required to select a child risk category and explain the process for obtaining assent and parental permission.

iStar maintains the currently approved study. With each amendment submission, the investigator is required to update the previously approved study to reflect the changes under review. iStar systematically records all changes and stores previous versions of the application and study documents in an accessible manner.

Among the documents available in iStar are:

- iStar submission (initial and continuing review)
- Informed consent and assent forms (if applicable, these documents are available in both approved and draft form)
- Scientific protocol
- Study grant
- Recruitment documents

- Surveys and questionnaires
- Approval documents from collaborating Institutions
- Ancillary committee approvals
- Reportable events and reports
- IRB and study team correspondence
- IRB approval notices
- Other documents related to IRB review

In addition to being a submission and document storage system, iStar creates historical records and provides audit trails of the IRB review process. All study-specific correspondence between the research team and the IRB are created and stored in iStar.

8.2 Criteria for IRB Approval of Research

In order to approve research, federal regulations (45 CFR 46.111) require that the IRB (reviewer or Full Board) determine that all of the following requirements are satisfied:

- Risks to subjects are minimized: (a) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (b) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB will not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

- Selection of subjects is equitable. In making this assessment the IRB must take into account the purpose(s) of the research and the setting in which the research will be conducted and must be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116.

- Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117.

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

- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, the IRB will ensure additional safeguards have been included in the study to protect the rights and welfare of these subjects. Refer to Chapter 14 – Vulnerable Subject Populations.

In addition to these regulations, the IRB must also consider:

- PI/study team qualifications, including credentialing and hospital privileges

- Adequacy of research description and methodology

- Certification that all study personnel have completed required training

- Conflict of Interest (PI and study staff)

- Subject recruitment

- Privacy and confidentiality

- Risk/benefit ratio

- HIPAA applicability and waivers

- Scientific merit
- Budget review
- California laws and university policies

Review of Scientific Merit

Scientific merit is a basic expectation of human subject research and is an integral part of the IRB review. It is not ethical to expose subjects to risk and inconvenience if the research has no merit. At HSC, the IRB takes into consideration any scientific review conducted by other committees or outside entities before the study was submitted to the IRB.

Federal regulations (45 CFR 46) as well as the Association for the Accreditation of Human Research Protection Programs (AAHRPP) require the IRB to review the scientific merit of proposals.

Peer or scientific review by USC institutional scientific committees such as the Cancer Center Clinical Investigations Committee and the Clinical Trials Unit (CTU), reviews by committees external to USC such as NIH cooperative groups, NIH study sections, sponsor review committee(s), and regulatory agencies such as the Food and Drug Administration provide assurance that experts have evaluated the study and found it meritorious. At HSC, for protocols that have not undergone peer/scientific review, additional reviewers with knowledge in the relevant discipline may be assigned to provide confidence in the scientific merit of the study. This process assures that in addition to all other review criteria scientific merit is properly addressed.

The IRB reviews all studies to ensure that:

- The research uses procedures consistent with sound research design
- The research design could allow the proposed research questions to be answered
- The risk/benefit relationship is acceptable
- The purpose and specific aims are clear and feasible, and the research will contribute to generalizable knowledge

Experts agree that the IRB should approve only research that is both valid (can answer questions posed) and of value. The IRB may request for an expert consultant to review a

proposed research project or defer to scientific review committees in order to determine whether a study has sufficient scientific value (merit) and/or if a study design places subjects at unnecessary risk. Before the consultant reviews the study, the IRB office will confirm with the consultant(s) that there is no potential conflict of interest.

Student research is expected to be reviewed by a dissertation committee for scientific validity. Further, projects that do not provide an actual benefit to society or have compelling scientific merit can still be approved by the IRB if all other approval criteria are met.

For **Department of Defense** sponsored research, review of scientific merit is required prior to initial IRB approval. In addition, any substantive amendment to approved research sponsored by DOD must undergo scientific review prior to the review by the convened IRB.

Review of Research Funds/Budget

Knowledge of adequacy of financial resources for proposed research is inherent in the IRB's responsibilities and obligations in the protection of human subjects. If research cannot be carried through to its completion, subjects may be put at risk. The PI must respond to IRB inquiries concerning financial resources. However, individual salary information does not have to be included in the study budget. The PI must also respond to IRB inquiries about financial payments to the study team for potential financial conflicts of interest (see USC Conflict of Interest policies). At HSIRB, clinical trials budgets are further scrutinized by the Clinical Trials Office.

Initial letters of award, and/or sponsor/donor documentation must be included in the IRB application. If a researcher is funded via private donor(s), researchers must set up an account with Contracts & Grants or the researcher's department/school must handle the disbursement of funds. In both cases, the IRB must be provided with funding documentation.

The IRB requires a copy of the grant/contract proposal; a copy of the final award letter (proof of funding) is not necessary. When donations from sponsors/donors support unspecified research, documentation to that effect must be uploaded to iStar. The IRB will not approve a study without required funding information.

8.3 Review of Exempt Research

To obtain an exempt determination, the investigator must submit an exempt iStar application with appropriate attachments. The PI indicates the exemption category believed to be appropriate [45 CFR 46.101(b)] and replies to all requests for revisions and/or clarifications requested by reviewers via iStar.

At USC, select IRB staff or designees as well as the Chair and Vice Chairs have the authority to approve exempt studies. Reviewers of exempt determinations conduct a review of the project to determine if it qualifies for exempt status according to IRB policy, human subjects research regulations, and ethical standards. To facilitate review, additional revisions may be requested by the IRB. If the study does qualify, the PI is notified and no further IRB review is needed.

When the study does not meet exempt criteria, the IRB staff and/or designee determines the appropriate level of review, notifies the investigator, and guides the investigator with resubmission at the required level. If exempt determination is unclear, the Chair, Vice Chair, or designee may assist with the determination. Exempt determinations are distributed to all IRB members electronically and acknowledged by each committee.

IRB reviewers have access to all necessary application materials in the iStar system, including:

- A completed iStar application with conflict of interest statement
- Proposed information sheet(s) and/or scripts as appropriate
- Surveys, questionnaires, or videos
- Letters of assurance or cooperation with research sites
- Relevant grant applications

  Recruitment materials and advertising intended to be seen or heard by potential subjects, including email solicitations

Amendments and Revisions to Exempt Research

Requirements for submission of proposed amendments in exempt research are different depending on whether the study is reviewed at the University Park IRB (UPIRB) or the Health Sciences IRB (HSIRB).

At the UPIRB, once a project is determined by the IRB to be exempt, changes (such as personnel, methodology/procedures, subject population, recruitment materials) that DO NOT affect the level of risk, level of IRB review, or the subject's willingness to participate DO NOT require further IRB review. However, when a proposed change increases the level of risk, the investigator is required to submit proposed revisions through the iStar amendment application.

In contrast, HSIRB requires investigators to submit modifications to previously approved exempt studies through an amendment in iStar. IRB approval of the amendment must be granted before any changes are implemented in the study. If a change is necessary to eliminate apparent immediate hazards to the research subjects or others, the investigator must promptly (within 30 days) inform the IRB of the change by submitting a reportable event in iStar. The IRB will review the change to determine that it was consistent with ensuring participants' continued welfare. The IRB approval letter sent to the investigator outlines this responsibility.

8.4 Review of Expedited Research

To submit a project for expedited review, the investigator must submit an expedited iStar application with appropriate attachments. IRB staff initially evaluates all submissions and may request changes/clarifications from the investigator. IRB staff then prepares a staff review that is forwarded to an expedited reviewer for review and approval. In the staff review the reasons why the submission meets expedited review criteria are noted by citing the appropriate expedited review category or summarizing the nature of the modification. The expedited reviewer is prompted to either concur or disagree with the staff recommendation for expedited processing and any related contingencies or necessary revisions.

The expedited reviewer has access to all necessary application materials in the iStar system, which includes the following:

- A completed iStar application with conflict of interest statement
- Investigator's or sponsor's protocol
- Proposed informed consent document(s) and/or script as appropriate
- Surveys, questionnaires, or videotapes
- Letters of assurance or cooperation with research sites
- Relevant grant applications
- Recruitment materials and advertising intended to be seen or heard by potential subjects, including email solicitations

The expedited reviewer is responsible for evaluating the project to ensure that the rights and welfare of human subjects are protected and that all criteria for IRB approval have been met. The expedited reviewer is also responsible for determining whether the study can be approved with or without changes and whether clarifications are required.

The reviewer may request review of the research by an expert consultant for issues which require expertise beyond or in addition to that available on the IRB committee. A determination that the consultant does not have a conflict of interest is made.

The expedited reviewer may send requests for clarification directly to the PI, or can forward requests to the PI through the assigned IRB staff member. If the application requires modifications, the IRB correspondence identifies the modifications that must be made by the investigator before the study can begin. The investigator's response to correspondence arising from expedited review procedures need only be evaluated by the expedited reviewer. In the event that the expedited reviewer makes a recommendation that is not accepted by the investigator, the expedited reviewer has two options: (1) Accept the investigator's justification for not incorporating the recommendation and proceed with the approval of the study; or (2) Reject the justification and forward the submission to the next Full Board IRB meeting for further consideration of the issue.

All studies meeting criteria for approval under the expedited criteria must meet the requirements for informed consent or its waiver or alteration (see Section 10.10 – Waivers of Informed Consent).

If the study is approvable, the approval notice indicates expedited review procedures were followed and notes the expedited review categories under which the approval was granted.

Information or proposed changes submitted in an amendment, adverse event, sponsor notification, or sponsor notification may disqualify a study from being approved under the expedited review procedure. In this situation, the study is forwarded to the full IRB for determination.

Expedited determinations and actions are distributed to all IRB members electronically and acknowledged by each committee.

Expedited Reviewers

Expedited review may be carried out by the IRB Chair, Vice Chair, or by an experienced IRB member formally designated by the IRB Chair. To qualify as an expedited reviewer, the IRB member, according to the judgment of the IRB Chair, must have the experience and education required to conduct expedited review.

Expedited reviewers may exercise all of the authorities of the IRB, except for disapproving the research (a research activity may be disapproved only after review by the full committee). If the reviewer and investigator cannot agree on the changes required to secure approval, the application will be sent to the convened IRB for review. The reviewer may refer the application to the Full Board for review at any time.

Although expedited review requires fewer steps than full committee review, it is not a lesser review process. All of the requirements for the protection of human subjects are applied equally in expedited review and the same requirements for informed consent (or its waiver or alteration) apply to expedited categories of research.

If a research study is found to be ineligible for expedited review, it will be added to the next possible full committee meeting agenda for review.

8.5 Review of Full Board Research

To submit a project for Full Board review, the investigator must submit a Full Board iStar application. The IRB staff reviews the application to ensure it is complete, and if necessary, will request revisions and/or clarifications from the investigator. The staff

review is available on iStar. The IRB staff schedules the study for the next available IRB meeting The IRB Chair or IRB Director selects primary and secondary (and tertiary when applicable) reviewers. The reviewers' comments, questions, and contingencies are posted in the iStar system and discussed during the Full Board meeting. Study materials and reviewer comments are available to all committee members.

The Full Board review process is described below:

- A majority of the members of the IRB and at least one non-scientist and one non-affiliated member (can be the same member with dual roles) must be present.
- If the required number of members is lost during a meeting no action may be taken until the quorum is restored.
- In order for a research project to be approved, it must receive the approval of a majority of the members present at the meeting.
- The IRB Chair reminds the IRB members of the requirement to disclose conflicting interests. The Chair polls the members present for any conflicting interests not previously declared or identified by IRB staff.
- IRB members cannot vote on a study if they are an investigator or member of the study team, if they significantly contributed to the design and conduct of the proposed study, if they meet the criteria for a financial conflict of interest, or if they have other interests that may affect their objectivity.
- A member with a potential conflicting interest may be invited to answer preliminary questions about a study, but then leave the meeting until the final vote is taken. The meeting minutes will record the name of any member who does not participate in the final vote on a study because of a conflicting interest.
- For studies involving subjects who may be vulnerable to coercion or undue influence, the IRB Chair, Director, or staff will ensure that one or more individuals who are knowledgeable about or have experience working with the subjects will review the study. These individuals may be current IRB members and/or consultants.
- For studies involving the recruitment of prisoners, the IRB Chair, Director, or Staff will ensure that a prisoner representative will be present at the meeting.

- A meeting may be conducted by conference call provided that each participating IRB member has received all pertinent material prior to the meeting and can actively and equally participate in the discussion of all protocols. Meeting minutes must clearly document that these two conditions have been satisfied and should specify which members were present via conference call.
- IRB meeting deliberations (UPIRB only) are tape recorded to assist with the drafting of meeting minutes and correspondence. Audiotapes of IRB meetings are maintained until the finalized version of the minutes is approved by the IRB.
- IRB meetings are scheduled at regular intervals appropriate to the amount of research requiring review and with sufficient frequency to ensure that the IRB can adequately oversee the progress of the research it has previously approved.
- Each protocol undergoing initial or continuing review will be discussed and voted upon separately.

Full Board Reviewer Assignments

The IRB uses a "primary reviewer" system for review of all new research proposals at its convened meeting. Members will be assigned studies for which they will be responsible for providing a detailed review. Reviewer assignments are made with the following goals in mind: to ensure review by a member with appropriate expertise and to equally distribute assignments. The expectation is that each IRB member will be familiar with every study on a meeting agenda.

The number of assigned reviewers differs according to the nature of the submission and whether previous peer review(s) for scientific merit is available (such as review by the USC Clinical Investigations Committee (CIC), the USC Clinical Trials Unit (CTU), NIH cooperative groups, NIH study sections, sponsor review committees, and regulatory agencies such as the Food and Drug Administration). Peer reviews provide assurance that experts have evaluated the study and found it meritorious. At HSC, for protocols that have not undergone peer/scientific review, additional reviewers with knowledge in the relevant discipline may be assigned to provide confidence in the scientific merit of the study. This process assures that in addition to all other review criteria scientific merit is properly addressed.

Primary and Secondary Reviewer Responsibilities

The IRB has developed comprehensive reviewer checklists/guidelines to assist IRB members and staff in performing thorough reviews. The checklists can be downloaded from the IRB website "Tips for IRB Submissions" page under IRB Reviewer Guidelines/Checklists (also refer to Appendix B). IRB staff and IRB members receive education on the reviewer checklists/guidelines and are encouraged to use them.

The primary reviewer should be knowledgeable about the medical or social-behavioral issues relevant to the protocol. The primary reviewer performs a detailed review of the protocol in order to ensure that the study is appropriately designed to protect subjects and to achieve the stated goals of the project. If primary reviewers do not believe they possess the required expertise, they must contact the IRB Chair or staff and request the study be assigned to another primary reviewer.

For the HSIRBs, the secondary reviewer is asked to focus most of the review on the documents that will be provided to subjects (informed consent forms, recruitment materials, questionnaires, and survey forms). The secondary reviewer should evaluate whether these documents clearly and accurately describe the nature of participation in order to ensure that potential subjects are able to provide truly informed consent. The UPIRB secondary and tertiary reviewers have the same role as a primary reviewer.

All reviewers are asked to upload a written review in iStar. In their written comments, reviewers identify human subjects protection concerns, explain the basis for raising those concerns, request modification to study documents, and ask for clarification or additional information. All assigned reviewers attend the IRB meeting and present their analysis to the Full Board committee. If a reviewer is unable to attend the meeting, another assigned reviewer or the IRB Chair will present the review to the committee. Even if written comments are provided by the assigned reviewers, the board might choose to defer discussion of a protocol until a time when the assigned reviewer can attend the meeting and present concerns in person.

Use of Consultant Reviewers

If the IRB Chair/Director determines that the IRB lacks the expertise necessary to review a particular study, the IRB will seek the services of an external consultant reviewer. An expert will be identified and invited to review the study as a consultant. The consultant will be required to disclose any possible conflict of interest to the IRB using the same

criteria applied to investigators as outlined in Section 13.6 – Investigator Conflict of Interest. Once it is confirmed that there are no actual or perceived conflicts of interest, a copy of the complete study submission and any reviews posted by the other reviewers will be sent to the consultant. The consultant will provide written comments to the IRB and may be invited to attend the meeting to discuss the protocol. The consultant cannot vote.

Meeting Materials – Full Board

The IRB staff electronically distributes all meeting materials to IRB members or their alternates through iStar. To ensure adequate time for review, the meeting agenda, study documents, and minutes to be approved by the board are sent to members approximately seven days before the meeting. Meeting materials available to IRB members for new study submissions are listed below.

- iStar study application
- Previous correspondence from study team and IRB
- Study protocol
- Grant application (including budget)
- Sponsor's sample informed consent documents
- Drug and device brochures
- Informed consent documents
- Child assent forms
- Surveys, questionnaires, and other instruments
- Recruitment materials
- HIPAA authorization forms and other documents required for medical research

A list of meeting materials for Continuing Review, amendments, and reportable event submissions are found in their respective sections in Chapter 9 – IRB Considerations after Initial Approval.

Projects Needing Verification from Sources Other than the Investigator

The IRB may determine that verification of required changes as well as study conduct need to be provided by sources other than the investigator. The IRB determines the appropriate sources and makes that part of the contingencies for approval. The criteria used by the IRB to make these determinations could include some or all of the following:

- Complex projects involving increased risk to subjects
- Projects conducted by investigators who previously have failed to comply with the requirements of the Health and Human Services (HHS) regulations or the requirements or determinations of the IRB, and
- Projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources

8.6 Sponsored Research and Ancillary Approvals

Other university approvals may be necessary before a study can begin, depending on the type of funding and the type of study. Funding and contract agreements are negotiated through USC Department of Contracts and Grants, which includes the Clinical Trials Office. The IRB application will inform the reviewer and/or investigator that additional approvals must be obtained. The ancillary approvals, encountered mostly at HSC and less frequently at UPC, are described below.

Funded Research

Department of Contracts and Grants

All research funds received from federal, state, and local government and/or private/foundations must be deposited with the Department of Contracts and Grants (DCG). The DCG:

- Serves as "gatekeeper" for acceptance, oversight and disbursement, and fulfilling government and university requirement

- Provides training and assistance to faculty and research administration staff
- Assists with proposal development, review, approval and submission
- Negotiates and accepts awards on behalf of the University
- Offers post-award administrative guidance
- Maintains the Sponsored Projects Data Information System (DCG Database)
- Provides support to University offices and committees in matters related to research policy and guidelines

Clinical Trials Office (Industry-funded)

The Clinical Trials Office (CTO) provides budget development and contract negotiation and execution for industry-sponsored research.

Medicare Coverage Analysis (MCA) and Consistency Review

CTO staff prepares the Medicare Coverage Analysis (MCA) for all clinical trials regardless of the funding source or Medicare eligibility. The MCA is used to identify and differentiate between costs that are study-related and those that are routine care. Routine care costs are independent from the study and would therefore be billed to Medicare, another insurer, or the subject. CTO verifies that the terms of "qualifying trials" are met before study costs are allocated.

The IRB staff works closely with CTO to ensure that language in the informed consent document and iStar application is consistent with the sponsor contract or Clinical Trial Agreement. CTO staff will modify and approve the language in the Financial Obligation and Compensation section of the iStar application as needed. This is accomplished using the "Review Consistency" activity.

If the investigator has addressed all the IRB contingencies before the CTO review is final, the IRB will approve the study but will not release the informed consent documents. The investigator cannot begin recruitment and enrollment until the CTO review is completed, the IRB confirms that the cost, injury, and compensation sections of the consent documents match the CTO language, and the IRB uploads the stamped consent documents in iStar. The IRB will notify investigators when the approved consent documents are uploaded and enrollment can begin.

Institutional Contract and Funding Agreements

At USC, the Clinical Trials Office and the Department of Contracts and Grants are responsible for funding agreements. All institutional contract and funding agreements meet established standards and include:

- A written agreement addressing medical care for research participants with a research-related injury, when appropriate
- A written agreement stating that the sponsor promptly reports to USC findings that could affect the safety of participants or influence the conduct of the study (for studies in which sponsors conduct site monitoring visits or conduct monitoring activities remotely)
- A written agreement that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to USC, when the sponsor has the responsibility to conduct data and safety monitoring
- A written agreement, before initiating research, that addresses plans for disseminating findings from the research and the roles that researchers and sponsors will play in the publication or disclosure of results
- A written agreement that the researcher or USC will be notified of the results in order to consider informing participants, when participant safety could be directly affected by study results after the study has ended

Ancillary Committee Reviews

Depending on the study, additional ancillary committee review and approval may be necessary before the study can begin. The IRB submission will trigger certain required approvals; however, some approvals are not linked to iStar and may be required after IRB submission depending on the study. Ancillary committees include:

- Institutional Biosafety Committee (IBC)
- Radiation Safety Committee (RSC)
- Stem Cell Research Oversight Committee (SCRO)

- Conflict of Interest in Research Committee (CIRC)
- Investigational Drug Pharmacy Services
- Pathology and Laboratory Services
- Clinical Trials Unit (CTU)
- Cancer Center Clinical Investigations Committee (CIC)

8.7 IRB Review and Determinations

Full Board Review

At a convened meeting, after all reviewers present their analyses of the study, the discussion is opened to all members. During the discussion, other members note omissions, raise and/or comment on issues, request clarifications, and make suggestions to improve the readability of consent and recruitment documents. When all members have the opportunity to voice their concerns and no further discussion is necessary, the board votes upon the study and makes one of the following determinations:

Approve

If the board determines that the study as written provides adequate protection of human subjects, the board will approve the study with no further changes.

Approve with Contingencies

The contingencies under Approval with Contingencies are not contingencies that impact the regulatory determination for approval. If the board finds that the application is "approvable" with modifications, clarifications, or verifications, the board will approve the study with contingencies that can be verified by a designated reviewer. The IRB may require the following as conditions of approval:

1) confirmation of specific assumptions or understandings on the part of the IRB regarding how the research will be conducted;

2) submission of additional documentation;

3) precise language changes to protocol or informed consent documents; or

4) substantive changes to protocol or informed consent documents along with clearly stated parameters that the changes must satisfy.

The IRB may designate the verification of satisfied contingencies to the IRB Chair, Vice Chairs, or an IRB member, without additional review by the Full Board. This process does not constitute an expedited review. Refer to Appendix I - Verification that IRB Contingencies were Satisfied for additional information.

Defer

If the board has serious concerns about the study, and/or requires significant modifications directly relevant to the criteria for regulatory determinations under 45 CFR 46.111 and/or 21 CFR 56.111, the board must defer a vote on the approval of the study. The subsequent response to request for significant modifications may not be reviewed using expedited procedures and must be reviewed by the Full Board. Examples of significant modifications include more than minor changes to the risks, research design and methodology, statistical analyses, data safety monitoring plan, provisions for protecting human subjects' safety and privacy, and informed consent document(s).

Table

If the board is unable to initiate a discussion of a study due to a lack of time, loss of quorum, or the absence of a reviewer, the board will table the discussion of the study for review at a subsequent meeting.

Disapprove

If the application describes research activities that may pose significant concerns for human subject safety with minimal prospect of benefit, or the risk/benefit ratio is deemed to be unfavorable, the board may disapprove the study.

An IRB member makes a motion for one of the above options; if another member of the IRB seconds the motion, the motion is voted upon. A majority of the members present at the meeting must vote in favor of the motion for passage [45 CFR 46.108(b) and 21 CFR 56.108(c)]. Discussion and/or deliberations of each study on the meeting agenda continues until one of the above motions is passed.

Expedited and Exempt Review

The IRB designated reviewer can make one of the following determinations:

- Determine that the study as written provides adequate protection of human subjects and approves the study (with no further changes). The IRB will approve a study only after determining that the proposed application contains sufficient information to address the criteria for IRB approval cited at 45 CFR 46.111 and 21 CFR 56.111.
- Find that the application is "approvable" after modifications, clarifications, or verifications and designate a reviewer (same reviewer, IRB Chair, Vice Chairs, another IRB reviewer, or IRB administrator) to verify that contingencies have been satisfied. Refer to Appendix I - Verification that IRB Contingencies were Satisfied for additional information.
- If the reviewer has serious concerns about the study, and/or requires significant modifications directly relevant to the criteria for regulatory determinations under 45 CFR 46.111 and/or 21 CFR 56.111, the expedited reviewer can refer the study for Full Board review.

Review of Response to Contingencies

When a study is approved with contingencies, the IRB designates a reviewer (same reviewer, IRB Chair, Vice Chairs, another IRB reviewer, or IRB administrator) to verify that contingencies have been satisfied.

- If the designated reviewer determines that the investigator has satisfied all conditions of approval, further IRB review is not necessary.
- If the reviewer determines that the investigator failed to adequately address the modifications requested by the IRB, the investigator's response may be returned to another member reviewer or to a Full Board meeting. The reviewer may request additional correspondence identifying outstanding concerns to be sent to the investigator by IRB staff.

- If the reviewer determines that the initial response and/or secondary correspondence from the investigator is inadequate, unacceptable, or raises new concerns, the study will be forwarded to the full IRB for further adjudication at the next possible IRB meeting.

Additionally, the following applies when changes to research are proposed after the IRB has approved the research with contingencies:

- If changes proposed are administrative/editorial in nature, no additional IRB review is needed and the changes can be reviewed as part of the verification process.
- If additional changes/procedures, which are listed in the expedited review categories under 45CFR 46.110, are proposed by the PI or designated reviewer, those changes may be reviewed by the IRB Chair/Vice-Chair/designated reviewer through an expedited review procedure.
- If changes are more than minor, increase risks to subjects, and/or impact any of the approval criteria under 45 CFR 46.111, those changes would require review by the full IRB committee.

This review process is applicable to review of response to contingencies after initial study submission, amendments, continuing review and reportable events.

8.8 IRB Correspondence and Investigator Response

IRB Correspondence

After each IRB meeting (or review by designated reviewer), the IRB staff forwards correspondence to investigators whose protocols were reviewed, notifying them of the action/status of their applications. The nature of the correspondence and the process by which an investigator's response is reviewed vary according to the decision made for the study.

- When the board (or reviewer) determines that the study as written provides adequate protections, the correspondence indicates the study is approved (with no further changes).

- When the board (or reviewer) finds that the application is "approvable" after modifications, clarifications, or verifications, the correspondence indicates the study is approved with contingencies.
- When a study is approved with contingencies, the IRB staff composes correspondence describing reviewers' comments and concerns and forwards it to the investigator. The investigator's response to the correspondence is then reviewed by the Chair/Vice Chair or designee.
- Correspondence indicates when the IRB or reviewer previously agreed that a response may be evaluated by a designated reviewer.
- When the IRB or reviewer has serious concerns about a study, or if significant modifications are required to ensure protection of human subjects, the correspondence indicates that the IRB will defer approval of the study until additional information is obtained from the investigator.
- For Full Board studies, when the board is unable to initiate a discussion of a study due to a lack of time or the absence of a reviewer, the correspondence indicates the board will table the discussion of the study for review at a subsequent meeting.
- When the application describes research activities that may pose significant concerns for human subject safety with minimal prospect of benefit, or the risk/benefit ratio is deemed to be unfavorable, the correspondence indicates the IRB's decision to **disapprove the study**. Investigator will have the opportunity to respond to the board in person or in writing [45 CFR 46.109(d) and 21 CFR 56.109(e)].

IRB correspondence includes all the information required by federal regulations and/or guidance. Generally, IRB correspondence for Full Board review studies is approved by the Chair before it is sent to investigators.

IRB correspondence with IRB determinations and the IRB's action will be sent to the investigator [45 CFR 46.109(d) and 21 CFR 56.109(e)]. When responding to the IRB's determinations or requests, the investigator may disagree with the board or reviewer, and provide written justification in support of their viewpoint. The IRB will then review the investigator's justification and make a determination. It should be noted, however, that the IRB has the final authority to approve or disapprove the research.

Investigator Response

During the IRB review process, all requests for modifications or further clarifications from the IRB are documented in a letter and sent to the investigator by IRB staff via iStar. The investigator's response to the IRB correspondence is evaluated in accordance with the requirement set forth during the initial review (reviewed by the Full Board, reviewed by an expedited reviewer, or verified by an IRB staff member). All correspondence between the IRB and investigators is recorded and stored under the history tab in the iStar application.

If the investigator believes requirements imposed by the IRB are unduly restrictive of the proposed research, the investigator can contest the requirements to the IRB. The investigator can outline the reasons why the proposed research procedures are already in compliance with USC policy and the applicable federal regulations and request that the IRB reconsider the requirement. If the IRB rejects the appeal, the investigator must comply with the IRB's restrictions or the research will not be approved. No other entities or officials at USC may override the IRB's decision to disapprove a study.

Other institutional entities or officials may determine that a study approved by the IRB cannot be conducted. Among the reasons for disapproval are issues of inadequate resources or university sensitivities.

8.9 IRB Meeting Schedules and Transfer of Jurisdiction

Meeting Schedule for Health Sciences IRBs

HSIRB 1 meets the first and third Thursday of each month. HSIRB 2 meets the second and fourth Thursday of each month. HSIRB 3 meets on the first and third Tuesday of each month. A calendar for submission and review dates is available on the HSIRB website http://oprs.usc.edu/hsirb/hsirb-deadlines/.

Meeting Schedule for University Park IRB

The full UPIRB meets the second Friday of each month. A calendar for submission and review cut-off dates is available on the University Park IRB (UPIRB) website http://oprs.usc.edu/upirb/upirb-deadlines/.

Transfer of Jurisdiction from UPIRB to HSIRB

Because the University Park faculty is predominantly on nine-month contracts, securing a quorum for the summer months may not always be an option. Additionally, there may be studies requiring biomedical expertise. Under these conditions, the University Park IRB (UPIRB), at their discretion, defers Full Board reviews to the Health Sciences IRB (HSIRB). The UPIRB Director sends a request to the HSIRB Chair to add studies to an HSIRB Full Board agenda. The UPIRB staff completes the staff review and the HSIRB staff adds the study to a HSIRB agenda. The UPIRB Director, UPIRB Chair, and/or UPIRB staff reviewer attend the HSIRB meeting. The HSIRB keeps the study under their jurisdiction until all contingencies (if any) are met or the study obtains final approval. If there is a need for a consultant, or expertise beyond that of the HSIRB members, the HSIRB Chair will secure the appropriate consultants.

8.10 Additional IRB Submissions

In addition to the IRB submissions described earlier in this chapter, there are other IRB submissions applicable to human subjects research. These IRB submissions include Continuing Review, Amendments, Significant New Findings and/or Information (SNIFs), Reportable Events, and Reports. These submissions are not discussed further in this chapter as they are described in Chapter 7 – Types of IRB Submissions and discussed as part of the IRB submission process in Chapter 9 – IRB Considerations after Initial Approval.

Primary Investigator and Self-experimentation

Application of submission for USC IRB review is required for human subjects studies entailing self-experimentation.

USC policy does not distinguish between self-experimentation and research on subjects who are recruited for a specific project. As part of its commitment to the protection of the rights and welfare of individuals participating in research, USC's Research Protection Program requires investigators who wish to act as participants in their own studies to submit for IRB review and approval - following standard procedures as outlined in the IRB policy. All human subject research must be reviewed to assure safety of those involved and the integrity of the research at the university. While researchers may be aware of the risks of self-experimentation, they may also be more willing to accept risks that are ill-advised. Application for review with the IRB office allows a neutral third party to raise concerns and/or propose measures to promote the welfare of researchers.

Chapter 9:

IRB Considerations after Initial Approval

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