Cambridge Health Alliance
Institutional Review Board (IRB)
Policies and Operations
Manual

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Abbreviations

The following abbreviations are used throughout his manual:

CAPA: Corrective and Preventive Action
CCO: Chief Compliance Officer
CDC: Centers for Disease Control and Prevention
CEO: Chief Executive Officer
CFR: Code of Federal Regulations
CHA: Cambridge Health Alliance
Co-I: Co-Investigator
COI: Conflict of Interest
Common Rule: Principals of 45 CFR 46 Subpart A[1]
CR: Continuing Review
DHHS: Department of Health and Human Services
DSMB: Data and Safety Monitoring Board
FDA: U. S. Food and Drug Administration
FD&C Act: Federal Food Drug and Cosmetic Act
FWA: Federalwide Assurance of Compliance
HIPAA: Health Insurance Portability and Accountability Act of 1996
IB: Investigator's Brochure
ICF: Informed Consent Form
IDE: Investigational Device Exemption
IND: Investigational New Drug
IO: Institutional Official
IRB: Institutional Review Board
JCAHO: Joint Committee on Accreditation of Healthcare Organizations
MA DPH: Massachusetts Department of Public Health
MGL: Massachusetts General Laws
MPA: Multiple Project Assurance
MSDS: Material Safety Data Sheet

[1] The "Common Rule" refers to 45 CFR Part 46, Subpart A, which were adopted in 1991 by most federal agencies in response to the convergent DHHS and FDA regulations and revised in 2018. Subpart A defines defies the Common Rule; the remaining Subparts were added subsequently and are not recognized as part of the Common Rule. However, when the Common Rule is referred to it is generally considered to include Subparts B, C, D, and E.

NCI: National Cancer Institute
NIH: National Institutes of Health
NSR: Non-Significant Risk
OHRP: Office for Human Research Protections[2]
PI: Principal Investigator
RSO: Radiation Safety Officer
SAE: Serious Adverse Event
SR: Significant Risk
UA: Unanticipated Event
UP: Unanticipated Problem

[2] Formerly the Office for Protection from Research Risks (OPRR).

A. Introduction

The purposes of this operations manual are:

- To provide the basic operational guidelines, polices, and procedures of the Cambridge Health Alliance (CHA; "the institution") Institutional Review Board (IRB) in accordance with 45 CFR 46 and 21 CFR 50, 56;
- To delineate the responsibilities of the Institutional Official for the CHA IRB, and the IRB office[3];
- To consolidate IRB guidelines, policies, and procedures contained in a variety of documents, the FWA, and various other documents relied upon by the IRB.

An IRB is a Federally mandated entity charged with ensuring the safety and welfare of study participants by applying ethical principles governing research involving human research subjects. At CHA, the ethical principles are applied regardless of the funding source.[4]

Research is defined as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR 46.102 (l)).

For FDA-regulated research, clinical investigation is defined as any experiment that involves a test article and one or more human subjects and that is either subject to requirements for prior submission to the FDA, or the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit (21 CFR 50.3(c)).

Human subject is defined as a living individual about whom a researcher obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens, or obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens (45 CFR 46.102) or an individual who is or becomes a subject (either a healthy human or a patient) in research, either as a recipient of the test article or as a control (21 CFR 50.3(g)).

Any person wishing to suggest a new or revised policy, procedure or form is invited to submit the suggestion in writing to the Chief Compliance Officer, along with a description of the rationale for the change. IRB policy revision and creation will occur on an as needed basis.

If a revised or new policy does not affect the function of the convened IRB or its decision-making, a drafted policy will be circulated for review and discussion among the IO, the IRB Chair, and the Human Research Protection and Research Integrity Manger. Policy decisions will be reached by consensus, not by vote. Such new or revised policies will be announced at the convened IRB meetings as relevant.

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[3] "IRB office" is used to distinguish between the IRB committee and the administrative office.

[4] DHHS regulations (45 CFR 46) apply to research involving human subjects conducted by DHHS or funded in whole or in part by DHHS. FDA regulations (21 CFR 50 and 56) apply to research involving products regulated by FDA. Federal support is not necessary for FDA regulations to be applicable. CHA uses DHHS regulations to inform for the review of all unfunded research conducted at CHA. As a result, typically, industry-sponsored, privately funded research, unfunded research, *etc.*, are subject to the same regulations as federally funded research.

Policies that affect the function of the convened IRB or its decision-making process will be drafted by the IO, the IRB Chair, and the Human Research Protection and Research Integrity Manger and will be voted on by the convened IRB. The vote will be recorded.

An overview of the structure, responsibilities, and membership of the IRB follows.

- The IRB
- IRB office
- Institutional Official (IO)

The IRB functions under FWA00000014, which was granted by the DHHS. The IRB operates under IORG0000446 (IRB00000760). Per 45 CFR 46.501, the IRB is registered as an OHRP/FDA entity.

The IRB is responsible for reviewing research involving human subjects at the institution to ensure that subjects' safety, rights, and welfare are protected in conformity with applicable regulations issued by the DHHS and the FDA, and other Federal agencies, as applicable.

The IRB also ensures conformity with applicable Massachusetts state and local laws and regulations regarding human subject protection that exceed the protection afforded under Federal law. In addition, guidelines and requirements imposed by the Institution that exceed Federal, state or local laws are applicable.

The IRB is organized under the Office of the Vice President and General Counsel.

The IRB typically convenes on a monthly basis, or as needed, to review research involving human subjects that is greater than minimal risk. In the event that there is no new research to be presented to a convened IRB and no studies that require continuing review by a convened IRB, the IRB Chair in consultation with other IRB leadership may cancel or reschedule a meeting.

The IRB office will facilitate the IRB's fulfillment of its review responsibilities and is overseen by the Chief Compliance Officer. It is staffed by other professional and support personnel.

CHA has designated the individual occupying the position of Chief Compliance Officer as the IO who oversees the activities of the IRB under FWA00000014.

1. Scope of IRB Review Responsibility

The IRB reviews all human subject research conducted at CHA. Research designed to include human subjects, tissues or materials from living humans, or data about humans must be formally reviewed and approved, or granted an exemption by, the IRB before the research begins, if any of the following are true:

- Institutions are “engaged” in human subject research when its employees or agents intervene or interact with living individuals for research purposes; or, obtain individually identifiable private information for research purposes.[5]

- An institution is considered to be "engaged" in human subject research whenever it directly receives a DHHS award to support human research. In such cases, the awardee institution is responsible for protecting human subjects enrolled in research funded by the award.

- The research is sponsored by CHA, including the following components, which are associated with the FWA:

    - Cambridge Hospital
    - Somerville Hospital
    - Whidden Memorial Hospital
    - Institute of Community Health
    - Physician’s Organization
    - Alliance Foundation for Community Health
    - Cambridge Public Health Commission
    - Cambridge Health Alliance

- The research is conducted by, or under the direction of, any health care personnel, employee, or agent of the institutions in connection with his or her institutional responsibilities, or by students under the formal guidance of an academic mentor(s).

- If an employee or agent of CHA conducts the research at his/her private office in accordance with the mission of the institution, CHA will consider serving as the site’s IRB.

- The research is conducted by, or under the direction of, any health care personnel, employee, agent, student, or affiliated individual or entity requiring access to, or using any property of, CHA facilities.

- The research involves the use of any of the institution’s nonpublic information (*e.g.*, paper or electronic medical records, research databases) to identify or contact existing or prospective human research subjects.

In some instances, particularly where data or material were not obtained for research purposes and contains no identifiers (10 August 2004, *Guidance on Research Involving Coded Private Information or Biological Specimens*) the research is not considered human subjects research, and is not within the scope of the CHA IRB review. In these instances, the IRB will make a determination that the research is not human subject research, and provide a signed letter to this effect to the investigator.

NOTE: In this manual where “IRB Chair” is used to indicate the person who will carry out an activity or a responsibility, it is understood that either the IRB Chair or his/her designee may carry out the activity or responsibility.

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[5] OPRR policy guidance, *Engagement of Institutions in Research*, issued 16 October 2008

2. IRB Membership

Per Federal regulation an IRB requires at least five (5) members and will represent a diversity of disciplines and varying backgrounds to promote the complete and adequate review of research activities conducted by the institution. The IRB shall be sufficiently qualified through the experience, expertise, and diversity of its members to promote respect for its advice and counsel in safeguarding the safety, rights, and welfare of human research subjects. In addition, the IRB shall have:

- At least one (1) member whose primary concentration is in scientific areas, such as a physician or scientist;
- At least 1 member whose primary concentration is in a nonscientific area, such as a lawyer, ethicist, member of the clergy, *etc.*;
- At least 1 member who is unaffiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

IRB membership lists, changes in IRB structure, and changes of IO will be maintained by the IRB office and updated and submitted to OHRP, as required. Membership will remain unpublished; however, the research community will know the identity of the IRB Chair and Vice Chair. At the request of the Principal Investigator (PI) or a member of a research team, *in lieu* of a membership roster, a letter attesting to the status of the FWAs and conformity with state law will be provided.

Recognized alternate IRB members may be used. IRB records will identify the member(s) for whom an alternate may substitute. A concerted effort will be made to ensure that the alternate's qualifications are comparable to the member for whom s/he is substituting. The meeting minutes will document when an alternate substitutes for a primary member. The alternate member will have received all materials distributed prior to the IRB meeting.

The IO, in consultation with the IRB Chair, will appoint IRB members. Residents will be eligible for IRB membership. The initial term of any appointment will typically be for 2 years and will be subject to re-appointment. At the conclusion of a term of appointment, a member may be appointed for an additional term, and may serve successive additional terms; a term limit will not be imposed. At the time of reappointment, members will undergo a general evaluation by the Chair and will be invited to share feedback. The IO will make reappointments based on recommendations from the IRB Chair. Consideration will be given to stagger membership reappointment. Note: Some members of the IRB pre-date this term of appointment policy; however, periodic re-evaluation will still occur.

The IRB Coordinator/Administrative Assistant will maintain a file pertaining to each IRB member. Each IRB member file should contain a copy of:

- Member’s letter of appointment or reappointment(s) to the IRB;
- Member’s résumé/CV at the time of appointment and reappointment;
- Other relevant correspondence relating to the member’s IRB service;
- Documentation of the completion of human subject protection education requirement(s) and any other relevant certificates of completion.

The files pertaining to IRB members are confidential and may be accessed by the IO, the IRB Chair, the IRB Vice Chair, the IRB office staff, and regulatory oversight personnel.

3. Roles and Responsibilities

This section discusses the roles and responsibilities of:

- IO
- IRB office staff
- IRB
    - IRB Chair
    - Members
    - Primary Reviewers
- *Ex-officio* Members

If, at any time, the IRB Chair, an IRB member, an IRB office staff person, or any other individual has concern that the IRB has been unduly influenced or has acted in a manner inconsistent with institutional policies or Federal regulations, the individual should report this to the Human Subject Protection and Research Integrity Program Manager for review and appropriate follow-up and action, as indicated. All such communications will be treated confidentially. The IO is responsible for oversight of any investigation and, as necessary, taking corrective and preventive actions to help eliminate recurrence.

The Institutional Official

The IO will be responsible for implementing the institution's FWA that all human subject research will be guided by the ethical principles of the Belmont Report, in accordance with the relevant regulatory requirements of 45 CFR 46 and with the human subject regulations or policies of any other relevant Federal, state, or local Department or Agency.

The IO, in consultation with others, appoints the IRB Chair and members.

The IO is also responsible for providing adequate resources, staff, security, and space to fulfill his/her commitment to ensure that the IRB office can perform its responsibilities and facilitate the effective and safe functioning of the IRB.

The IO will oversee the activities of the IRB through the following procedures:

- Appointments
    - The IO will appoint the IRB Chair; Co-Chairs may be appointed.
    - The IO may appoint one or more Vice-Chairs who will be responsible to the IO and IRB Chair and who may assist the IRB Chair in the performance of his/her duties.
    - The IO in consultation with the IRB Chair shall make appointment of new IRB members.
    - The IO may appoint *ex-officio* members to the IRB.
- The IO may remove or replace the IRB Chair or IRB members.
- The IO will make efforts to attend at least 1 convened IRB meeting per year.

- The IO will be recognized as non-voting *ex-officio* members of the IRB.
- Consider recommendations made by the IRB Chair/VC related to a request for IRB authorization and render the final determination.
- The IO may receive monthly status reports/updates from the IRB Coordinator/Administrative Assistant or designee regarding the preparation of meeting minutes and such other information as may be requested to evaluate the functioning of the IRB. The Human Research Protections and Research Integrity Program Manager and the IRB Coordinator/Administrative Assistant will meet with the IO as needed to discuss IRB and IRB office operations. The Chair will attend as needed.
- The IO may decide to increase or decrease the number of committees as needed to ensure the adequate and efficient review of the research submitted to the IRB.
- Proposed revisions to the IRB Operations Manual are subject to the approval of the IO, with recommendations from the Chair.

The IRB Office

The primary function of the IRB office is to enable the IRB to carry out its review responsibilities.

- Human Research Protection and Research Integrity Program (HRPP) Manager
- IRB Coordinator/Administrative Assistant

Human Research Protection and Research Integrity Program Manager

The HRPP Manager is responsible for ensuring that the IRB and CHA are in compliance with applicable regulatory requirements regarding human subject protections and oversees and implements activities to maintain and enhance the principles and practice of human subject research at the direction of the IO with input from the IRB Chair. These activities include education, creation and update of requisite policies and procedures related to human subject research, and development of future initiatives to further this mission. This position reports to the IO.

The HRPP Manager will generally have the following responsibilities related to the IRB:

- Provide ethical and regulatory guidance as a non-voting *ex-officio* member of the IRB; serve as a regulatory resource for institutional leadership, investigators, and co-workers about the conduct of human subject research;
- With the IO and IRB Chair develop and implement policies and procedures to maintain or enhance the function of the IRB and the institutional human research protections program;
- Direct, supervise, and lead research education initiatives for the CHA research community;
- Interface with inspectors in the event of a Federal or internal audit/inspection;
- Record and prepare IRB meeting minutes, including attendance, votes, and recusal. The vote on IRB minutes will typically occur at the next scheduled meeting; the IO will receive a copy of all IRB meeting minutes as distributed by the IRB Coordinator/Administrative Assistant;

- Coordinate the revision of this manual as directed by the IO, as needed;
- Update internal forms and documents to adhere to applicable state and Federal regulations and institutional policies and procedures;
- Process research non-compliance and provide analysis and recommendations regarding research non-compliance; facilitate the investigation of potential research non-compliance in consultation with the IRB Chair and oversee the reporting of research non-compliance to the IRBs;
- Pre-review submissions to the IRB office to ensure that submissions are minimally acceptable for IRB review assignment;
- In consultation with the IRB Chair, assign IRB members to act as Primary and Secondary Reviewers;
- Interface with regulatory authorities (*e.g*. OHRP, FDA) for the potential reporting of research non-compliance, involuntary suspensions and terminations, and reportable serious adverse or unanticipated events (SAE, UP);
- Orient and train new IRB members, in consultation with the IRB Chair;
- Prepare new study notification to a PI of IRB decisions for new studies reviewed by the convened IRB, typically within two (2) weeks of the IRB meeting;
- Maintain IRB member files;
- Update OHRP/FDA IRB registration/the FWA.

IRB Coordinator/Administrative Assistant

The IRB Coordinator/Administrative Assistant assists and supports the IO, IRB Chair, and HRPP Manager execute their responsibilities related to IRB operations. The IRB Coordinator/Administrative Assistant will follow IRB policies and will generally have the following responsibilities:

- Develop, execute, and revise as needed, processes and procedures to carry out IRB policies;
- Process all incoming mail, login protocols to the IRB database, and perform a preliminary screening of submissions to ensure required documents are present and applications are complete, accurate, and compliant with institutional policy;
- Communicate pre-review comments from the HRPP Manager to the PI and facilitate administrative processing;
- Facilitate the review, follow-up, and approval of expedited reviews, including prepare written correspondence to PIs in follow-up to review of submitted applications, as needed;
- Maintain complete, accurate, and organized IRB files and database;
- Process, facilitate, track, and document requests related to IRB authorizations and communicate decisions to the researcher/institutions involved in the request, including maintaining accurate related paper and electronic files;

- Prepare IRB meeting agenda and assist the HRPP Manager with IRB meeting follow-up;
- Prepare notification to a PI of IRB decisions for amendments and continuing review applications reviewed by the convened IRB, typically within two (2) weeks of the IRB meeting. Letters should be forwarded to the HRPP Manager for review before being sent to the Chair/Vice-Chair/Designated Reviewer for signature.
- Ensure that notifications to the IRB are accurately recorded on a monthly basis (*e.g.*, in-office expedited review of submissions). A list of the preceding month's approvals will be transmitted to IRB members prior to the next IRB convened meeting;
- Transmit a courtesy reminder to the PI regarding continuing review submission, per CHA policy.

4. IRB Meeting Minutes

In accordance with Federal regulations, meeting minutes will be prepared after each IRB meeting. The content of the minutes will be in sufficient detail to provide, among other, the following information:

- Meeting attendance — includes voting members, *ex-officio* members, and non-members;
- The time the meeting began and ended;
- Actions taken;
- The basis for requiring changes in or disapproving research;
- A written summary of the discussion of controverted issues and their resolution;
- Specific regulatory findings (*e.g.*, vulnerable populations, off-label use, significant/non-significant risk);
- The votes (for, against, and abstaining) for each agenda item;
- Recusals of IRB members or guests due to potential conflict of interest; and
- Whether any proposed changes constitute substantive changes and require re-review by the convened IRB for approval, or whether the changes are not substantive and may be reviewed and verified via expedited review by the IRB Chair or designee.

A recording may be made of each meeting to facilitate the preparation of written minutes. If a recording is made, upon IRB vote to approve the meeting minutes, recordings will be discarded. The minutes will be transmitted to members electronically.

A vote shall be taken at each meeting regarding the IRB approval of the minutes from the previous meeting. Proposed modifications to the minutes must be voted on by the IRB and will be recorded; the minutes will be revised accordingly for the IRB files. Only those members who attended a meeting in question may suggest modification to, and vote on, the minutes.

5. The IRB

The CHA IRB committee is comprised of the following:

- Chair
- Members
- *Ex-Officio* members

The IRB typically meets monthly, or as needed. The IRB may meet on a more or less frequent basis to accommodate the type, volume, or complexity of research. The proceedings and discussions at a convened IRB meeting are to be held in the strictest of confidence. In the event a meeting is cancelled, monthly notifications (*e.g.*, in-office expedited review, non-compliance notifications, SAE reports) will be transmitted to members at the next meeting.

Conflicts of Interest

No member may participate in review activities of any research in which the member has a potential conflicting interest, except to provide information as requested by the IRB. Such members will be present only for the presentation and discussion of the research, and then only to provide information that enhances the IRB's ability to protect subjects. At the IRB Chair's discretion, potentially conflicted members may be recused from the presentation and/or discussion, as well.

The member with the potential conflict will be required to leave the room for the deliberation and vote. A member who is the PI, a Co-investigator, recruits to the study, or has a potential or perceived conflict of interest in the research will be excused from the room during the deliberation and vote. Such recusals extend to the IRB Chair, IRB staff, as well as any non-member guests and/or observers.

Content Experts

If the IRB reviews a protocol requiring expertise beyond**,** or in addition to, that available on the IRB, an individual(s) with experience in such areas will be invited to serve as a non-voting consultant. A motion to involve a consultant may be made by any member at a convened meeting; however, involvement of a consultant must be made by majority vote of the members present. A consultant may also be engaged at the discretion of IRB leadership prior to initial presentation of a protocol.

IRB Chair

The Chair will be appointed by the IO and must have demonstrated an understanding of the regulations governing human subject research, awareness of the ethical considerations raised by such research, and a commitment to the highest standards of research integrity and human subject protection.

The IRB Chair will receive salary support for his/her work.

The IRB Chair has the following responsibilities, among others:

- Chair IRB meetings, or delegate the responsibility to a designee, as necessary;
- Be a resource to provide leadership, recommendations, education, guidance, and mentorship to other IRB members and the research community;

- With the IO and the HRPP Manger, develop, provide input on, and carry out policies and procedures necessary to maintain or enhance the function of the IRB and protections of human subjects;
- Be a resource to, and enhance communication between, investigators and the IRB;
- Provide recommendations and nominations of new IRB members;
- At the time of member reappointment, provide evaluation feedback to the member and the IO.
- Consult with the IO and the HRPP Manager regarding the composition of the IRB as needed to ensure adequate and efficient reviews and performance;
- Serve as a signatory for IRB correspondence;
- Provide review and determination regarding:
    - Whether a project constitutes human subject research, is QI, etc.,
    - Verify exemption from 45 CFR 46
    - Expedited review of research per 45 CFR 46, 21 CF 56
    - Amendment or modification to research during a study's approval period, and other submissions provided by investigators
    - SAEs and UPs
    - Response(s) to IRB requests
    - Potential research non-compliance
    - Request for waiver of HIPAA research authorization
    - Request for HIPAA review preparatory to research
    - Emergency use review
    - Notices of voluntary closure to accrual, suspension, and termination
    - Request for IRB authorization agreement
- Act as a Primary Reviewer of research presented to the convened IRB;
- Provide input and guidance on policies, procedures, processes, etc., for effective and efficient IRB function;
- The IRB Chair must complete all mandatory human subject protection education requirements established by CHA and is expected to participate in periodic research education teaching activities;
- Act in accordance with all institutional human research policies.

IRB Vice Chair

The Vice Chair(s)'s duties reflect the duties of the IRB Chair and support the Chair. The IRB Vice Chair fulfills these, and other, duties as designated by the IRB Chair.

The IRB Vice Chair has the following responsibilities, among others:

- Chair IRB meetings, as needed;
- Be a resource to provide leadership, recommendations, education, guidance, and mentorship to other IRB members and the research community;
- With the IO and the HRPP Manager, develop, provide input on, and carry out policies and procedures necessary to maintain or enhance the function of the IRB and protections of human subjects;
- Be a resource to, and enhance communication between, investigators and the IRB;
- Provide recommendations and nominations of new IRB members;
- At the time of member reappointment, provide evaluation feedback to the member, the IO, and the Chair.
- Consult with the IO, the Chair, and the HRPP Manager regarding the composition of the IRB as needed to ensure adequate and efficient reviews and performance;
- Serve as a signatory for IRB correspondence;
- Provide review and determination regarding:
    - Whether a project constitutes human subject research, is QI, etc.,
    - Verify exemption from 45 CFR 46
    - Expedited review of research per 45 CFR 46, 21 CF 56
    - Amendment or modification to research during a study's approval period, and other submissions provided by investigators
    - SAEs and UPs
    - Response(s) to IRB requests
    - Potential research non-compliance
    - Request for waiver of HIPAA research authorization
    - Request for HIPAA review preparatory to research
    - Emergency use review
    - Notices of voluntary closure to accrual, suspension, and termination
    - Request for IRB authorization agreement
- Act as a Primary Reviewer of research presented to the convened IRB;
- Provide input and guidance on policies, procedures, processes, etc., for effective and efficient IRB function;
- The IRB Vice Chair must complete all mandatory human subject protection education requirements established by CHA and is expected to participate in periodic research education teaching activities;
- Act in accordance with all institutional research policies.

IRB Members

IRB Members have the following responsibilities, among others:

- New members will undergo orientation and will typically observe the proceeding(s) of a convened IRB meeting(s) prior to formal appointment. Orientation will be documented.
- Complete all mandatory human subject protection education requirements established by CHA prior to serving as a voting member of the IRB and complete ongoing training on an annual and/or more frequent basis, as needed.
- Review materials on the IRB agenda and participate in the discussion of the studies at the convened IRB meeting. Materials will typically be distributed to members, including the IO, at least 7 days before the meeting. Circumstances may arise whereby materials are forwarded to IRB members fewer than 7 calendar days prior to the meeting, *e.g.*, addendum to the agenda, revised or additional materials provided by the PI. The agenda will be comprised of each research proposal and related documents (including ICFs, Investigator's Brochure if applicable, recruiting information, *etc.*).
- Review the IRB file of the protocols(s) she/he is assigned to review at the convened IRB meeting. Members are encouraged to do this when reviewing amendment and continuing review submissions to be presented to the convened IRB. The Reviewer may contact the IRB office to arrange a time to review the pertinent file(s) in advance of the IRB meeting. A complete copy of the IRB file for all studies on an agenda is available in the IRB office for review by IRB members prior to a meeting.
- Information Required for New Study Review
    - For new studies, each IRB member will receive a copy of the following information submitted by investigators approximately 7 days prior to an IRB meeting:
        - Protocol
        - Site-specific information
        - IRB Forms
        - Proposed ICFs
        - Drug(s), compound(s), and/or device information
        - All written information containing materials provided to subjects including, but not limited to, telephone script(s), interview text, questionnaire(s), survey instrument(s), advertisement(s), and contact letter(s).
        - Recruitment materials (letters, advertisements, postings, e-mail announcements, *etc.*)
        - HIPAA documentation.
- Information Required for Continuing Review (CR)

  Each IRB member will receive a copy of the following information before any study is presented to the convened IRB for continuing review:

    - Continuing Review form
    - Approved ICFs
    - Any tracked documents if amendment or modification is proposed at the time of CR.

- Information Required for IRB Notification

  The IRB will receive notification of the following events in a monthly compilation:

  - Exempt status determinations,
  - Expedited initial review approval,
  - Expedited CR approval,
  - Expedited modification/amendment approval,
  - Emergency use review,
  - Non-compliance,
  - Involuntary suspension or termination actions taken by the IRB Chair,
  - Any event deemed reportable to a regulatory Department or Agency,
  - Any other information as deemed necessary by the Chair.

- Each member is expected to attend a majority of the IRB meetings during the calendar year. Members are expected to remain throughout the duration of the entire meeting, except in the event of a potential COI, and are expected to actively participate in the discussion of research presented to the IRB. Only those members who attended a meeting in question may amend and vote on the meeting minutes.

- Each member will be expected to conduct initial reviews of research and/or continuing reviews and/or modifications to approved research and present the review to the convened IRB along with recommendations for approval, modification, or disapproval. Assignments will take into account each member's expertise and experience.

- To facilitate a timely and complete review, members are to communicate with the study PI (or designee) to request clarification or verification. Communication with the PI should occur prior to the meeting so that the review process may continue as scheduled. Members are expected to provide a copy of any electronic mail exchanges, as it pertains to the study under review, or a written summary of any meeting/telephone conversation(s). Members are expected to provide a summary of salient issues discussed as they pertain to the research under review.

- At the IRB meeting, each protocol will be individually presented, reviewed, discussed, and vote on as the IRB Coordinator/Administrative Assistant records information for the minutes. The IRB will decide upon one of the following actions by a majority vote of the members present:

  - Approval
  - Approval with Stipulation(s)
    - Substantive changes
    - Not substantive changes
  - Deferral
  - Disapproval
  - Tabled
  - Withdrawn

- Each member may review submissions that qualify for in-office expedited review (e.g., new exempt and expedited studies, expedited continuing review applications, proposed amendments). Functions, procedures, etc., will be similar to those outlined for convened IRB meeting review, except, no member may disapprove any study when reviewed via expedited review procedures.

It is the Reviewer's responsibility, with help from the IRB Chair and/or Vice Chair to assure that the PI's submission provides sufficient information to enable the IRB to make an informed judgment about whether and under what conditions to approve the protocol. In the event that the protocol and/or ICF(s) raise(s) issues that the IRB requires additional information or clarification, the Reviewer is to contact the PI or his/her designee prior to the meeting for the necessary information or clarification and corresponding revised documents, as indicated.

One week before the IRB meeting, an agenda comprised of each research proposal, and related documents (including the ICF, recruiting information, *etc.*) is to be distributed to members by the IRB Coordinator/Administrative Assistant. The Reviewer is also to carefully review the ICF(s) together with the protocol and any other related documentation to ensure that the ICF(s) accurately reflect the study procedures in the protocol, is of sufficiently simple readability, and contains all of the required elements of informed consent. The Secondary Reviewer should complete an internal institutional checklist to help ensure that the required elements of consent are present. A Secondary Reviewer will be assigned to each new study that is reviewed by the convened IRB. His/her responsibility and focus will be on the ICF content and readability.

It is the responsibility of the Reviewer to attend the IRB meeting with a complete, type-written presentation/summary of a study describing any suggested changes to the protocol, ICF(s), *etc.* To aid in the presentation, the Reviewer is encouraged to prepare a visual presentation; appropriate audiovisual equipment will be available at IRB meetings. If ICF revisions will be recommended, the Reviewer is to provide a notated ICF or a separate document detailing the specific changes required.

The Reviewer will lead the presentation and discussion of the research at the IRB meeting and make recommendations regarding approval, modification, deferral or disapproval of the protocol, as well as any suggested revisions to the ICF(s), *etc.*, and make a recommendation whether the recommended changes are substantive in nature and require re-review by the convened IRB, or are not substantive in nature and may be reviewed and verified via expedited review procedures. These recommendations are presented in the form of a motion that is seconded and voted on at the meeting.

As mentioned above, a member will be assigned as a Secondary Reviewer for each new study presented for initial review at a convened IRB meeting. The Secondary Reviewer will focus on the content, accuracy, readability, etc., of the ICF. S/He will present his/her review at the meeting, including any recommended changes. A notated copy of the ICF reflecting requested changes will be provided by the Secondary Reviewer, if indicated.

In the event that a Reviewer is unable to attend a meeting, he/she is responsible for providing a detailed written summary of the study, potential issues of concern for discussion, if any, and his/her recommendations for IRB action to the IRB Chair, who may, at his/her discretion, present it at the IRB meeting.

In the event that a PI requests that the IRB reconsider a stipulation, the original or most recent Reviewer will typically present the request for reconsideration at a convened IRB meeting (see 8. Request for Reconsideration). In the event that a prior Reviewer is not available, the IRB Chair will present the protocol him/herself or may assign a new Reviewer.

Reviewer forms exist to help assist IRB members ensure that the required elements of review are documented and present. The Reviewer is expected to complete the requisite review form(s), sign them, and at the conclusion of the IRB meeting leave it for the IRB Coordinator/Administrative Assistant.

Subsequent to the meeting, the Reviewer is responsible for reviewing the portion of the minutes of that meeting that pertain to the protocol(s) that he/she reviewed and presented, and for requesting any changes in the minutes to ensure accuracy.

Ex-officio Members

Holders of specific offices will be appointed as non-voting *ex-officio* members of the IRB. *Ex-officio* members will be appointed in recognition of their expertise and mission as it relates to the institution's human research programs. The *ex-officio* members will be non-voting members. The person holding the following offices will be non-voting *ex-officio* members of the IRB:

- Chief Compliance Officer
- HRPP Manager

When present at a convened IRB meeting, *ex-officio* members will not count toward the meeting quorum.

6. Transition to the 2018 New Final Rule

After the New Final Rule goes into effect in January 2018, all new studies reviewed by the IRB will be subject to the New Final Rule. Policies related to those reviews may be found elsewhere in this manual.

Those studies that were approved under the pre-2018 Rule will be eligible for transition after the New Final Rule takes effect. In most cases, the IRB will consider transition at the time of the first continuing review after the New Final Rule takes effect. IRB Reviewers will evaluate each study approved under the pre-2018 Rule and determinate and document whether the study will be transitioned to the New Final or whether it will remain under the pre-2018 Rule.

If a study is not transitioned to the New Final Rule, the Reviewer's rationale will be documented and the decision communicated to the PI in a written letter signed by the IRB Reviewer. The pre-2018 Rule will continue to apply to the research.

If a previously approved study is transitioned to the New Final Rule all regulatory elements of the New Final Rule will apply, including all new consent-related requirements. Subjects previously or currently enrolled in the study will not be required to give consent again under the new consent process or execute the updated ICF. Subjects who enroll in a study after the research has been transitioned to the New Final Rule must follow the new consent process, execute the revised ICF, etc. Policies related to consent may be found elsewhere in this manual.

If a previously approved study is transitioned to the New Final Rule and the IRB Reviewer determines that continuing review will still be required, the rationale and justification must be documented in his/her review, which will be retained in the IRB study file and will be communicated to the PI in a written letter signed by the IRB Reviewer. Factors that may lead an IRB reviewer to require continuing review when not otherwise required by Federal regulation include factors such as the funding source, the PI's research non-compliance history, the PI's research experience, including the PI's research experience with a given study population. Policies related to continuing review may be found elsewhere in this manual.

Application of Additional Regulations Depending on Federal Funding

In accordance with Federal regulation, for each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form (ICF) used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal website that will be established as a repository for such ICFs.

If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal website (e.g. confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

The ICF must be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

Additional Federal regulations, Directives, and Instructions that apply when Department of Defense (DOD) personnel will be recruited to a human subject research study or when a human subject research study is funded or supported by a DOD component through a grant, contract, cooperative agreement, of other arrangement. DOD components include, but are not limited to:

- Department of Defense
- Department of the Army
- US Army Corps of Engineers
- Department of the Navy
- US Marine Corps
- Pentagon Force Protection Agency
- Department of the Air Force
- US Air Force Academy
- Defense Intelligence Agency
- Defense Advanced Research Projects Agency (DARPA)
- Office of Naval Research
- US Naval Academy
- US Naval Observatory
- US National Guard
- US Coast Guard
- National Security Agency
- US Military Academy (West Point)

Researchers are expected to be aware of and compliant with the additional requirements. Consideration should be given to these requirements when planning a research project funded or supported by a DOD component, as they may require additional time, resources, *etc.*, for the planning, review, and IRB approval process.

<u>Education Requirements</u>

All personnel involved in the conduct, review, or approval of human subject research that is supported by the DOD or a DOD component must complete initial and ongoing human subject education training. The DOD-specific component supporting the research may evaluate CHA's training requirements to ensure that each

individual has undergone appropriate training based on the nature of the research. The PI is responsible for ensuring that all members of a research team have completed the appropriate education requirements as mandated by DOD policy.

Contracts and Awards

In addition to requirements established by the funding agency, investigators who conduct human research supported by the DOD or its components must comply with contracting requirements and processes of CHA's Office of Sponsored Research.

DOD Definitions/Key Terms

32 CFR 219: Title 32, Part 219 of the Code of Federal Regulations; it is the regulation adopted by multiple Federal departments and agencies governing human subject research. These regulations are the DOD's implementation of DHHS regulations 45 CFR 46, Subpart A ("The Common Rule").

DOD Instruction 3216.02 "Protection of Human Subjects and Adherence to Ethical Standards in DOD-Supported Research" (DODI 3216.02): This Instruction establishes policy and assigns responsibilities for the protection of human subjects in DOD-supported programs to implement 32 CFR 219.

Title 10 United States Code (USC) Section 980 "Limitation on Use of Humans as Experimental Subjects:" Imposes limitations on waiving informed consent when using DOD appropriated funds. 10 USC 980 is applicable only to DOD funded research involving a human being as an experimental subject. Funds appropriated to the DOD may not be used for research involving a human being as an experimental subject unless:

1. The informed consent of the subject is obtained in advance; or
2. In the case of research intended to be beneficial to the subject, the informed consent of the subject or a LAR of the subject is obtained in advance.

The Secretary of Defense may waive the prohibition in this section with respect to a specific research project to advance the development of a medical product necessary to the armed forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws.

This means that research involving deception, individuals with impaired decision-making capacity, or research being done under emergency conditions where the subject is not able to provide consent may not be possible.

Intervention and Interaction: An intervention includes both physical procedures by which data are gathered 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. Examples include, but are not limited to, a physical procedure, a drug, manipulation of the human subject or his/her environment, withholding of an intervention that would have been undertaken if not for the research purpose, or communication such as a survey or interview. Note: Research involving use of human subjects for testing of chemical or biological agents is generally prohibited by 50 U.S.C. 1520a subject to possible exceptions for research for prophylactic, protective, or other peaceful purposes.

Minimal Risk (32 CFR 219.102(i)): The probability and magnitude of harm or discomfort anticipated in the research are not greater in and or themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The phrase "ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests" shall not be

interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (*e.g.*, emergency responder, pilot, soldier in a combat zone) or having a medical condition (*e.g.*, frequent medical tests or constant pain).

Research Involving Human Subjects: An activity that includes both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information, or activities covered by section 32 CFR 219.101 (including exempt research involving human subjects) and DODI 3216.02.

Research Involving a Human Being as an Experimental Subject: An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects. This definition relates only to the application of section 980 of Reference (g) (see DODI 3216.02); it does not affect the application of part 219 of Reference (c) (see DODI 3216.02). This definition does not include activities that are not considered research involving human subjects, activities that meet the exemption criteria at section 219.101(b) of Reference (c) (see DODI 3216.02), and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

Children

Research involving human subjects conducted or supported by the DOD that recruits children to be subjects must meet the additional relevant protections of Subpart D (45 CFR 46).

Compensation

The following limitations on compensation for military research subjects apply:

- Federal personnel may not be paid by any sources other than their regular salaries while on duty, including compensation for research participation, except for compensation for blood draws (up to $50 per blood draw).
- Federal personnel may be compensated for research participation when not on duty, in a reasonable amount as approved by the IRB, according to local prevailing rates and the nature of the research.

Informed Consent

For "research involving a human being as an experimental subject," informed consent must be obtained from the subject with the following exceptions:

- Consent may be provided by the experimental subject's LAR if the research intends to benefit the individual subject. Note: The determination that the research is intended to be beneficial to the individual subject must be made by the IRB.
- A waiver of consent may be approved by the Assistant Secretary of Defense (ASD) for Research and Engineering (R&E) only for research that meets all of the following conditions:
    - The research is necessary to advance the development of a medical product of the U.S. Military Services.
    - The research may directly benefit the individual experimental subject.
    - The research is conducted in compliance with all other applicable laws and regulations.

Note: The ASD may delegate the waiver authority described above to the Heads of the Office of the Secretary of Defense and DOD components if they have appropriate policies and procedures in their management plans. This authority is further delegable only to a DOD Component official who is a Presidential Appointee with Senate Confirmation.

International Research

For international research, the IRB will consider the subject population, cultural context, and the language understood by the subjects during review. In addition, the IRB will require that all local laws, customs, and practices are followed. The PI will be required to submit documentation of the local IRB or ethics review as applicable. The IRB will consult with General Counsel and/or outside consultants (with expertise in the region/country being studied) as necessary.

Multi-site or Collaborative Research

When conducting multi-site or collaborative research, a formal agreement between organizations is required to specify the roles and responsibilities of each party, including the following:

- Statement of work and/or brief description of the research.
- Provisions for oversight and ongoing monitoring.
- Reporting requirements.
- Document retention.

Pregnant Women, Fetuses, or Neonates

For research involving pregnant women, fetuses, or neonates, the following additional requirements apply:

- When applying Subpart B (45 CFR 46), the phrase "biomedical knowledge" should be replace throughout with "generalizable knowledge"
- The applicability of Subpart B is limited to research involving pregnant women that is greater than minimal risk and that includes interventions or invasive procedures for the woman or the fetus, or to the research involving fetuses or neonates

Prisoners

For research involving prisoners, the following additional requirements apply:

- DOD-supported research involving prisoners cannot be reviewed by the expedited procedures.
- When a previously-enrolled research subject becomes a prisoner, in addition to the IRB Policy on Research Involving Prisoners, all of the following are also required:
- The convened IRB, upon being notified that a research subject has become a prisoner, will promptly re-review the study to ensure that the rights and well-being of the now prisoner-subject are not in jeopardy.
- The convened IRB may only approve a change to the research to allow the prisoner-subject to continue in the study if the subject can continue to provide consent, s/he is capable of meeting the study requirements, the terms of confinement do not inhibit the ethical conduct of the research, and there are no other significant issues preventing the study from continuing as approved.
- IRB approval is limited to allowing the specific prisoner-subject to continue in the study and does not allow recruitment of additional prisoners.

- The IO and DOD-specific Component office must review and concur with the convened IRB's approval to change the research to include the prisoner-subject.

Prisoner of War

Prisoners of war are individuals under the custody and/or control of the DOD as defined in the "General Convention Relative to the Treatment of Prisoners of War of August 12, 1949." Research involving prisoners of war is prohibited.

Records

Records maintained by non-DOD institutions that document compliance or noncompliance with DODI 3216.02 shall be made accessible for inspection and copying by authorized representatives of the DOD at reasonable times and in a reasonable manner as determined by the supporting DOD Component.

Reporting

The following must be promptly (within 30 days) reported by the PI to the DOD-specific component's human research protection official or office:

- When significant changes to the research are approved by the IRB
- Results of continuing IRB review
- Change(s) in reviewing IRB
- Notification by any Federal department, agency, or national organization that any part of the HRPP is under a "for-cause" investigation involving DOD-supported research
- Serious and/or continuing noncompliance
- Any unanticipated problems involving risks to subjects or others for DOD-supported research
- Any suspension or termination of DOD-supported research

Research Monitor

If the IRB determines that the research involves more than minimal risk to human subjects, the IRB must approve an independent research monitor by name. Monitors shall possess sufficient educational and professional experience to serve as the subject/patient advocate; they may be physicians, dentists, psychologists, nurses, or other healthcare providers capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. The monitor may be an ombudsman or a member of the data and safety monitoring board. The research monitor may be identified by an investigator or appointed by the IRB or IO; s/he must be independent of the team conducting the research involving human subjects. There may be more than one research monitor (*e.g.,* if different skills or experiences are necessary).

The research monitor will have expertise consonant with the nature of risk(s) identified within the research protocol; his/her role is to protect the safety and well-being of the human subjects. The research monitor may perform oversight functions (*e.g.,* observe recruitment, enrollment procedures, and the consent process for individuals, groups or units; oversee study interventions and interactions; review monitoring plans and reports of unanticipated problems involving risks to subjects or others; and oversee data matching, data collection, and analysis) and report their observations and findings to the IRB or a designated official.

The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have authority to stop a

research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities. The IRB or HRPP official shall communicate with research monitors to confirm their duties, authorities, and responsibilities.

The Heads of the Office of the Secretary of Defense (OSD) and DOD components may waive the requirement to have a research monitor on a case-by-case basis when the inclusion of a research monitor is not necessary to provide additional protections for human subjects. Waiver authority may be delegated to a DOD official, as described in the component's HRPP management plan, but not at or below the position of the institution's DOD IO.

Research related injury

The IRB and investigators will ensure that consent disclosures for research-related injury follow the requirements of the DOD-specific component. Investigators are expected to work with their DOD Project Coordinator/Program Officer to identify such requirements.

Surveys

Surveys performed on DOD personnel must be submitted, reviewed, and approved by the Department of Defense after the research protocol has been reviewed and approved by the IRB.

Scientific Review

When new non-exempt research involving human subjects and substantive amendments/modifications to previously approved non-exempt research is presented, the IRB review must consider the scientific merit of the research. The IRB may rely on outside experts to provide an evaluation of the scientific merit.

Waiver of Informed Consent

See Informed Consent above.

Additional Requirements

The following protections for military research subjects will be implemented to minimize undue influence:

- Superiors (*e.g.*, military and civilian supervisors, unit officers, and noncommissioned officers) are not permitted to influence the decisions of their subordinates (*e.g.*, junior enlisted personnel and equivalent civilians).
- Supervisors may not present at the time of recruitment or during the consent process for members of units under their command.
- Superiors will have a separate opportunity to participate in the research.
- An independent ombudsman will be present when recruitment involves a percentage of a unit.

References

32 CFR 219: DOD Protection of Human Subjects

Department of Defense Instruction 3216.02 (DODI 3216.02): Protection of Human Subjects and Adherence to Ethical Standards in DOD-Supported Research (Version November 8, 2011)

Title 10 United States Code Section 980: Limitation on use of Humans as Experimental Subjects

45 CFR 46: Department of Health and Human Services Protection of Human Subjects

7. Other Related Offices and Interrelationship

The IRB operates independently of, but in coordination with, other institutional offices/committees. The CHA IRB renders an independent decision whether to approve, require modification to, or disapprove a study, and has oversight of all human subject research conducted at, supported by, or otherwise subject to regulation by any Federal department or agency that has adopted the human subject regulations.

The CHA Academic Council is scheduled to meet on a monthly basis and serves in an oversight and advisory capacity to the IRB.

Scientific review is accomplished through a two-fold approach: By a Department Chief's review of an application prior to PI submission. The review is documented by the Chief's required signature, provided the application meets an acceptable standard. The second step is through IRB review. For any greater than minimal risk study, the convened IRB also plays a role in scientific merit evaluation.

It is the responsibility of the PI to ensure that all applicable offices have reviewed, approved, or granted and documented the necessary waiver(s) prior to initiating human subject research.

Sponsored Research Administration/Office of Sponsored Research

Sponsored Research Administration (SRA)/the Office of Sponsored Research (OSR) staff review all research agreements with Federal, foundation, industry, or non-profit sponsors. This internal review ensures that the award terms are in compliance with institutional policies and other applicable requirements. OSR is also responsible for overseeing and managing clinical trial registration (i.e., clinicaltrials.gov) and ensuring research education and conflict of interest requirements are satisfied based on terms of agreement with a grant or contract. Please refer to SRA/OSR-specific policies.

Investigational Drug Service (IDS)

To ensure the CHA Department of Pharmacy, and the IDS, is aware of the human subject research that involves investigational or marketed drugs, typically a CHA pharmacist serves on the CHA IRB.
The IRB advises the PI/research team to contact the CHA Department of Pharmacy during protocol development to ensure that all associated issues are addressed. In addition, study budgeting involving an investigational drug or device should include IDS-related fees.

General IDS responsibilities include ordering, processing of, storing, inventorying, accounting for, and dispensing study drugs. Additional services include creating randomization schemes, randomizing subjects, and adhering to applicable state and Federal requirements.

If a PI does not intend to employ the IDS services, the PI is responsible for documenting approval for waiver from the IDS and adhering to regulations and Institutional policies and procedures regarding drug storage, security, accounting, dispensing and disposal.

The IDS maintains policies and procedures regarding IDS Functions. Please also refer to the Department of Pharmacy Fee Schedule for Managing Investigational Medicines.

The CHA Department of Pharmacy maintain the Massachusetts Controlled Substances Researcher Registration required by the Massachusetts Department of Public Health, as needed.

Radiation Safety Committee and Radiation Safety Officer (RSO)

Any study that involves *research-related* ionizing radiation exposure (*e.g.*, x-rays, including Computed Tomography (CT) scan, bone densitometry, mammography, nuclear medicine procedures, radiation therapy procedures whether they use radioactive sources or external beam (accelerators)) will require review by the convened IRB, as per Federal regulation. Such proposed research is to be reviewed by the CHA institutional RSO. The RSO will conduct an assessment of the proposed exposure and will determine if the exposure and the associated language describing it in the protocol and ICF, including potential associated risks, are acceptable as submitted or require revision/modification. If revision is necessary, the RSO will detail the necessary changes. In order for the IRB to approve a study involving research-related radiation exposure, the proposed exposure and associated language in the ICF describing the exposure and associated risks must be found to be acceptable by the RSO.

If a study involves *clinically indicated* ionizing radiation exposure that is unrelated to study participation Investigators are advised to specifically address this in the proposed protocol at the time of initial submission. If such information is absent from the protocol at the time of review, the IRB will seek the input of the RSO and/or PI. This could result in review delays.

Internal Audit/Quality Assurance (QA)/Quality Improvement (QI)

QA/QI programs help to ensure researcher and institutional compliance with Federal and State regulations governing human research and institutional policies and practices. As a result, such programs help assure subject safety and scientific integrity of a research study, and improve overall study performance.

CHA is dedicated to supporting safe, compliant, high quality research. As a result, the CHA QA/QI program concentrates on education and support of PIs and research team members involved in the conduct of human subject research. CHA expects continuous QA and QI of ongoing research to be conducted, both by the study team and internal and external monitors, to enhance the CHA research enterprise and promote a culture of compliance. Periodically CHA QA/QI personnel will perform random internal audits of human subject research conducted by CHA personnel.

To assist CHA researchers, numerous guides and tools have been developed to help organize and monitor research. Researchers are strongly encouraged to use the documents made available, which are updated and revised periodically, or create their own documents to manage and monitor studies.

Among the documents are reference templates, study management templates, subject-related templates, and drug and device accountability templates.

Studies may be selected for audit for a variety of reasons, including:

- Routine evaluation (not for-cause),
- Directed (for-cause) audit may occur at the request of the CHA IRB or the IO,

- To respond to non-compliance findings, or
- Suspicion or report of serious or continuing non-compliance with Federal or State regulations or institutional policies or procedures.

In selecting studies for routine evaluation audits, matters such as the level of risk associated with participation, enrollment of vulnerable populations, and prior compliance issues associated with a study/investigator will be factors in the selection.

All members of a study team are expected to comply fully with any internal or external audit. Failure to do so may be viewed as non-compliance and processed in accordance with the institutional research non-compliance policy outlined elsewhere in this document or may be subject to other disciplinary actions.

After a protocol is identified and selected for audit, written notification will be sent to the PI with a copy sent to the Department Chair. The PI will be contacted, typically within 1 week of the delivery of the initial notification, to make arrangements for the audit, including a meeting date and time to review documents. With the PI's permission, arrangements can be made through the clinical research coordinator or other qualified designated research staff. Routine audits will be scheduled at a mutually agreeable time, preferably within 1 month of the audit notification. "For Cause" audits will typically be scheduled within 2 weeks of the audit notification being sent to the PI.

Prior to the audit, the PI will be requested to provide a list of all study participants, as applicable. To ensure subject confidentiality the list will be limited to participants' initials or unique identification number and their date of study enrollment.

From this list, the auditor will select several subject files for audit. The list of selected subjects will be provided to the PI so that all records containing information relevant to the study may be assembled, *e.g.*, research records, clinic charts, hospital records. Access to all selected subjects' records and associated documents should be provided to the auditor. At the time of the audit, additional records may be requested for review.

In the case of a "for cause," or directed, audit the auditor may elect to review 100% of the research subjects' records. In cases where the safety of a research subject may be in immediate jeopardy, the auditor may request a research subject's name and other identifying information to expedite the review of the subject's medical record, if applicable.

As part of audit preparation, the auditor will review the IRB study file, including related IRB meeting minutes.

The following are typically performed as part of any internal audit:

- Review of study records, including eligibility criteria and screening procedures. Review of any management or monitoring logs used by the study team.
- Review of study procedures to ensure they are performed in accord with the IRB-approved protocol, Federal regulations, and CHA policies.
- Review of on-site record keeping.
- Review of electronic records, as applicable.
- Review of test article accountability, as applicable.

Observation of the informed consent process may also occur.

Internal auditors will instruct the PI to **promptly** report to the IRB any events identified during an audit that may represent serious or continuing non-compliance or may be an unanticipated problem that may involve risks to human subjects or others.

Auditors may suggest process improvements and/or make recommendations to assure compliance. Referral to education tools and resources may also be made by the auditor.

A summary of the results of any QA/QI audit will be presented to the convened IRB. A standard report will be issued to the PI and his/her Department Chief.

Participant Outreach; Department of Community Affairs (CAF)

The CHA CAF helps CHA address the needs of the community through outreach efforts and innovative community health programs. Through these efforts the institution reaches populations that may not have access to the health care system, informing them of health care services and helping reduce barriers to care. These efforts to engage, educate, and improve the health of our communities use a collaborative approach by working with individuals, community groups, non-profit agencies, and public health departments. Included in this commitment is research. Education opportunities are offered to research subjects, prospective subjects, and community members to also enhance their understanding of human research conducted at CHA.

CHA also achieves this outreach through a webpage dedicated to research on the CHA website. Among the resources on the Research website are Frequently Asked Questions (FAQs), research administration contact information, and research-related links. Subjects can inquire about community-based research initiatives through these resources, communicate a complaint, concern, or questions, or provide input and/or feedback on research participation. In addition, presentations are periodically made to community organizations.

Outreach activities are informally evaluated periodically and updated or modified, as needed.

Harvard Catalyst

CHA is a participating institution of the Harvard Catalyst, a consortium founded in 2008 of Harvard hospitals and resources dedicated to advancing clinical research. The Harvard Catalyst provides a vast array of research resources to investigators, including the ability to network with others with common interests throughout the entire Harvard community.

Among the resources of the Catalyst are tools that facilitate clinical research, education and training opportunities, pilot funding, core facilities, and numerous other services.

A core component of the Catalyst is that the Harvard Catalyst Regulatory Knowledge and Support Program and IRBs covering more than 20 Harvard Catalyst-participating institutions developed an electronic cede review process and form to help facilitate IRB review of multi-site human studies. The form may be used for any multi-site studies that involve at least 1 Harvard Catalyst participating institution. Each participating IRB makes the decision on a protocol-by-protocol basis whether to rely on the review of another IRB (to cede the review) or to conduct its own IRB review.

8. IRB Authorization and Reliance Agreements

Requests that CHA engage in an IRB Authorization or Reliance Agreement are carried out by the IRB Coordinator/Administrative Assistant under the oversight of the IO. When CHA is asked to cede IRB oversight as part of an IRB authorization agreement, various factors may influence the decision, including:

- The research activity that will occur at CHA and whether CHA is engaged in research, as defined by Federal guidance.
- The potential risk associated with the activity that will occur at CHA,
- The CHA PI's research compliance history, and
- Information about the institution, PI, etc., of the proposed IRB of record.

On a case-by-case basis additional information may be gathered and/or may influence a decision to cede IRB review.

When CHA is asked to assume IRB oversight for another site(s), the following will be among the points that impact the decision whether CHA will agree to be the IRB of record for other sites:

- Detailed information regarding the activity that will occur at each site,
- Information about the qualifications/experience of the study team members at each site,
- Consideration of the facilities with respect to the level of risk associated with the research activity to be performed at each site.

Again, on a case-by-case basis and based on the specifics of the IRB Authorization or Reliance Agreement, additional information may be gathered by the IRB Coordinator/Administrative Assistant and/or may influence a decision to accept IRB oversight responsibility.

Information required will be gathered by the IRB Coordinator/Administrative Assistant and forwarded to the IRB Chair or Vice Chair for consideration of the request to cede or accept oversight. S/he will make a recommendation based on the information provided, which will be forwarded to the IO, who will render the final decision.

Based on the specifics of an agreement, the IRB Coordinator/Administrative Assistant will ensure that CHA responsibilities outlined in an agreement are satisfied. This will be done by requesting from the other site(s) all required information and verifying its receipt or by sending any required information to the other site(s).

B. IRB Operations and Procedures

The IRB is scheduled to meet monthly, or as needed. The IRB may meet on a more or less frequent basis to accommodate the volume or complexity of research. The proceedings and discussion at a convened IRB meeting are to be held in the strictest of confidence.

The IO may decide to increase or decrease the number of IRBs as necessary to ensure the adequate and efficient review of the submitted research.

The type of IRB review conducted is dependent on the research activity.

This section discusses the following types of operations and review procedures:

- Case reports
- Research versus Quality Improvement

- 3. Not Human Subject Research
- 4. Determination of Exempt Status
- Initial Review
    - Expedited
    - Convened IRB review
- Continuing Review
    - Expedited
    - Convened IRB review
- Modification of Previously Approved Research
    - Expedited
    - Convened IRB review
- Emergency use review

All human research that is not deemed by Federal regulation to be excluded or exempt from IRB review is subject to initial and, as applicable, continuing review either at a convened meeting of the IRB or by expedited review procedures, if eligible under applicable regulations.

After initial IRB review and approval investigators are expected to submit/report the following to the IRB:

- Continuing review, as applicable per Federal regulation
- Amendments/changes to the study protocol or changes in study activity (e.g., closure of the study to enrollment)
- UPs
- SAEs
- New information that may affect a subject's willingness to continue participation
- Deviations from the protocol
- Monitoring reports
- Non-compliance
- Termination notification

1. Case Reports

A case report or a case series is a retrospective analysis of 1, 2, or 3 clinical cases intended to broaden information for medical or educational purposes. Generally, reporting on up to 3 cases does not strictly meet the Federal definition of research.

While CHA does not require IRB review and approval if 3 or fewer patients' records will be accessed, the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, which specifies how protected health information (individually identifiable health information) may be used and disclosed, does apply. Depending on circumstances and details in a report, written authorization from the patient(s) may be required. The CHA IRB office and/or HIPAA Privacy Officer should be contacted and consulted prior to initiating work in such a situation.

CHA considers a retrospective analysis of more than 3 patients' medical records to be research as defined by Federal regulation and requires IRB review and approval prior to beginning the work, as well as meeting HIPAA requirements.

Irrespective of the number of records reviewed, if identifiers are removed from a case report prior to the case report being submitted to a journal, an author may be exempted from obtaining signed authorization from a patient discussed in a case report. Redaction of identifiers should be performed by a member of the CHA workforce. The author is responsible for ensuring compliance with patient privacy, institutional policies and practices, and Federal regulations.

Photographs or illustrations with identifiable features may not be included in a case report (*e.g.*, a patient's face, tattoo, or other identifying feature should not be visible). The author is also responsible to ensure that a case(s) described in a report is not so unique or unusual as to be possible to identify a patient(s) in a case report.

If an author seeks to publish a case report that is not de-identified to HIPAA standards, or if the potential exists that a patient could be identified or likewise could identify him/herself or a family member (*e.g.*, the condition or diagnosis is distinct or identifiable features appear in photographs), then the HIPAA Privacy Board should be consulted and explicit authorization obtained from the patient to use identifiable information. If a patient is deceased, authorization for the use of identifiable information is to be obtained from the personal representative of the patient's estate.

2. Human Subject Research or Quality Improvement (QI)

Please refer to CHA policy A-COM-0006 (Definition of Research versus QI) for details of this policy, including applicability, definitions, procedures, etc.

Whenever there is uncertainty as to whether a project constitutes human subject research, the project leader should contact the IRB office to request guidance. Personnel are reminded that there are serious consequences to researchers and the institution for not following CHA policies and Federal regulations when conducting research.

3. Not Human Subject Research

In accordance with guidance issued by the Office for Human Research Protections, revised on 16 October 2008, *Guidance on Research Involving Coded Private Information or Biological Specimens*, certain projects involving coded private information or human biological specimens that is conducted or

supported by DHHS may be determined to not be research involving human subjects. Investigators are encouraged to evaluate whether a proposed project constitutes human subject research and are expected to seek IRB input and guidance for a final determination if there is any uncertainty. A determination will be made by the IRB Chair or designee and communicated in a signed written letter to the PI.

Some DHHS conducted or supported research involving coded private information or specimens may be subject to FDA regulations. The FDA regulatory definitions of human subject (21 CFR 50.3(g), 21 CFR 56.102(e)) and subject (21 CFR 312.3(b), 21 CFR 812.3(p)) differ from the definition of human subject under DHHS regulations at 45 CFR 46. In accordance with the guidance document, the IRB may not apply the guidance to research regulated by FDA that involves coded private information or specimens.

Interpretation and application of this issue may be obtained from the IRB office and the OHRP guidance referenced above.

4. Determination of Exempt Status

In accordance with Federal regulation some human subject research may be exempt from regulations. However, under no circumstances is the PI to determine the exempt status of his/her research; the CHA IRB requires that all research involving human subjects must be submitted for review, regardless of the possibility of exemption.

A decision to grant exempt status will be made by the IRB Chair or designee and communicated in a signed written letter to the PI.

Form(s) and Process for Determining Exempt Status

For research that meets the regulatory requirements of exemption, the PI is to submit a completed and signed *Request for Exemption* and any additional required or applicable information.

Requests for exemption will be submitted to the IRB office and will undergo internal administrative pre-review per office procedures prior to the application being forwarded to an IRB member for review.

If the research is not granted an exemption from IRB review, the PI will be advised of the need to submit other relevant documents for review by the IRB, as directed by the IRB reviewer. The IRB reviewer is expected to document the appropriate category of exemption and any relevant findings.

If a project is granted exemption, that determination will be sent to the PI in a written letter signed by the IRB reviewer. If the PI proposes to make any change to the project once an exemption is granted, the proposed change is to be submitted in writing to the IRB for review to ensure that the study still qualifies for exemption. When an exemption is granted, the PI will be advised of the need to obtain IRB approval prior to changing the project. The PI will also be instructed to notify the IRB office in writing when the research is terminated to ensure accurate IRB records. Projects granted exemption are not subject to continuing review requirements; however, the IRB Coordinator/Administrative Assistant will perform an annual check-in with the PI to ensure that the study remains active and ongoing or may be terminated. Details of this appear elsewhere in this manual.

5. Initial Review

This section contains the following information concerning expedited and convened IRB review:

- Initial Review
  - Expedited
  - Convened IRB review
    - Quorum of the Membership
    - Deliberation and Voting Procedure
    - Preliminary Review
    - Primary Review
    - Actions of the IRB
    - Responses to IRB
    - Establishment of a Subcommittee
    - PI Request for Reconsideration

Expedited Review

Per Federal regulations, some research[6, 7, 8] may be reviewed and approved through expedited review procedures at the time of initial review. FDA regulation does not include research on behavior or characteristics of groups or individuals such as studies of perception, cognition, game theory, or test development in its list of research activities that may be reviewed through expedited review procedures, because the FDA does not regulate those types of studies.

Expedited review procedures may be used when the proposed research involves no more than minimal risk as defined by Federal regulation. Use of expedited review procedures allows the IRB Chair or a designee to exercise the authority of the convened IRB, therefore not requiring the research to be presented at a convened IRB meeting. However, the IRB Chair or the designee may not use expedited review procedures to disapprove a study; such an action can only be taken by the convened IRB.

After implementation of the New Final Rule, new expedited studies undergoing initial review will not be required to undergo continuing review. If, however, the IRB reviewer determines that a study must undergo continuing review, s/he must document his/her rationale and justification for requiring continuing review, including the frequency with which it is to occur.

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[6] Categories of Research that May be Reviewed by an Institutional Review Board through an Expedited Review

[7] Office for Human Research Protections (OHRP) Guidance on the Use of Expedited Review Procedures dated 11 August 2003

[8] Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure, 09 November 1998

Form(s) and Process for Determining Expedited Review

A PI may request expedited review; however; the appropriateness of expedited review will be determined by the IRB Chair or designee. Even if proposed research qualifies for expedited review, the IRB Chair or designee retains the option to forward a request for expedited review to the convened IRB.

The PI is to submit a completed and signed Expedited Review form, a copy of the proposed research protocol, a statement as to the applicability of HIPAA, and any questionnaires, advertisements, *etc.*, to be used in the research.

Requests for expedited review will be submitted to the IRB office and will undergo internal pre-review per office procedures prior to the application being forwarded to an IRB member for review. The IRB reviewer is expected to document the appropriate category for expedited approval and any relevant findings.

If expedited review procedures do not apply, the PI will be advised by the Reviewer or IRB staff of the need to submit any other relevant documents for review by a convened IRB, or if the requisite forms for convened IRB review are already present, the application will be forwarded to an IRB meeting agenda.

Research team members engaged in research that is reviewed and approved using expedited review procedures are required to complete the mandatory institutional human subject research education requirements and comply with the institutional conflict of interest policy.

Convened IRB Initial Review

All human subject research that is not eligible for exemption or expedited review will be presented to the convened IRB.

Quorum of the IRB

Convened IRB review takes place at a meeting where a quorum of the IRB is present. A majority of the members is required for a quorum; majority is defined as half of the IRB membership plus 1.

In rare instances, and in accordance with a 28 March 2000 OPRR memorandum and FDA guidance (Federal Register, Volume 46, No. 17, page 8967, 27 January 1981) a member may participate via telephone conference call and be considered "present" provided that each participating IRB member has received all pertinent meeting material prior to the meeting, and s/he can actively and equally participate in the discussion of all protocols. In such an instance, the meeting minutes will clearly document that those 2 conditions have been satisfied in addition to the usual regulatory requirements (*e.g.*, attendance, initial and continued presence of a quorum, including at least one non-scientist member; actions taken by the IRB; the vote on such actions; discussion and resolution of controverted issues).

Per Federal regulations, the quorum must include at least 1 physician/scientist and at least 1 member whose primary activities are in nonscientific areas. A member who is not present for the deliberation and vote of an agenda item may not be counted as part of the quorum with respect to that item. Should the quorum fail during a meeting (*e.g.*, those with conflicts being excused, early departures, a non-scientist not present) the meeting will be stopped and no further discussion or votes taken unless the quorum is restored.

Deliberation and Voting Procedures

The discussion of each agenda item is typically led by the IRB Chair and the Primary Reviewer, with a dedicated presentation given by the Primary Reviewer. At the end of the discussion, a motion will typically be made by the Primary Reviewer and a vote taken (for, against, abstention) and recorded for the meeting minutes. Each study presented for initial review, continuing review, or modification to a previously approved protocol on the IRB agenda will involve an IRB vote and will be presented, discussed, and voted on separately.

Preliminary Review

IRB staff will conduct a preliminarily review of an IRB application for overall completeness. The application will also be reviewed to verify the requisite IRB forms are present and completed. The level of completeness will determine if the application needs to be returned to the PI or if the PI/the research team should be contacted to obtain missing documents or the IRB review process is ready to begin. All efforts will be made to request missing forms or documents prior to the application being placed on an IRB agenda.

Typically, at least 7 days before the meeting materials will be distributed electronically to all members expected to attend the IRB meeting. Addenda to the agenda, revised or additional materials provided by the PI will be forwarded to IRB members as soon as possible. The submitted materials for each research proposal (including ICF, recruiting information, *etc.*) will be distributed to members. The IRB staff may notate components of the application with questions, comments, or suggested or preferred language, as appropriate and part of preliminary review, which will be given to members.

Primary Review

Prior to the IRB meeting, the IRB member assigned as the Primary Reviewer will be responsible for reviewing the application and ensuring that the submission provides the necessary information to enable the IRB to make an informed judgment about whether and under what conditions it may approve the protocol. In the event that the protocol or ICF raises issues that are likely to require further information or clarification, the Primary Reviewer is expected to contact the PI prior to the IRB meeting to obtain the necessary information or clarification.

The Primary Reviewer will also review the ICF(s) together with the protocol to ensure that the ICF(s) contains all of the required elements of informed consent. The ICF must adequately describe the research design and purpose, the procedures to be performed or followed, and if applicable their relationship to standard treatment for the subject's condition, as well as the risks, benefits and alternatives to participation in the study. The Primary Reviewer is expected to come to the IRB meeting with a complete summary describing, in detail, any suggested changes to the protocol, ICF, or other research study instruments.

The Primary Reviewer is responsible for presenting the protocol to the convened IRB and is expected to contact the PI prior to the IRB meeting to address and resolve any issues identified during the review. The Primary Reviewer is also encouraged to use visual aids as necessary for the presentation (*e.g.*, Microsoft Word or PowerPoint presentation).

The Primary Reviewer, with the Chair and/or Vice-Chair, will lead the discussion at the IRB meeting. The Primary Reviewer's recommendations regarding approval, modification, deferral, or disapproval of the protocol, as well as any suggested revisions to the ICF(s), *etc.*, will be recorded. If ICF revisions are recommended, the Primary Reviewer is to submit a notated ICF or a separate document detailing the specific

changes required. In the event that the primary reviewer is unable attend the meeting, he/she is responsible for providing a written summary of the study, the issues raised during the review, if any, and his/her recommendations for IRB action to the Chair, who may at his/her discretion present it at the IRB meeting.

As mentioned elsewhere in this document, a member will be assigned as a Secondary Reviewer for each new study presented for initial review at a convened IRB meeting. The Secondary Reviewer will focus on the content, accuracy, readability, etc., of the ICF. S/He will present his/her review at the meeting, including any recommended changes. A notated copy of the ICF reflecting requested changes will be provided by the Secondary Reviewer, if indicated.

Subsequent to the meeting, the Primary Reviewer shall be responsible for reviewing that portion of the meeting minutes that pertain to the protocol(s) that he or she previously presented/reviewed, and for requesting any changes to the minutes to ensure accuracy.

6. IRB Actions at Initial Review

In accord with Federal regulations, as applicable (45 CFR 46, 21 CFR 56), and institutional policy, research proposals will not be approved unless all of the following criteria for approval are satisfied:

- Risks to subjects are reasonable in relation to anticipated benefits (In evaluating risks and benefits, the IRB should 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 should not consider possible long- range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.);

- Risks to subjects are minimized;
- Selection of subjects is equitable;
- Informed consent will be sought and documented by each subject or his/her LAR or will be waived in accordance with Federal regulation
- All required forms, correspondence, and other documents are complete, signed and dated, and submitted to the IRB;
- ICF(s) contain all required elements and information;
- Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- There are adequate provisions to protect the privacy of subjects and to maintain the privacy and confidentiality of data;
- Instruction and/or informational sheet(s) are available to be given to the research subjects, as appropriate;
- Appropriate safeguards have been included to protect populations likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

At IRB meetings each protocol will be reviewed and discussed with any controverted issues, and their resolution, recorded. The motion will typically be made by the Primary Reviewer, may be amended as necessary, and will be seconded by another voting member. The potential actions of the IRB are delineated in other sections of this Operations Manual. All IRB actions will be documented in correspondence sent to the PI and verified by the signature of the IRB Chair or designee.

Letters to PIs that communicate IRB determinations will include a reminder that, among other points, changes to the protocol or ICF must be reviewed and approved by the IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to subjects.

The IRB will decide upon one of the following actions by a majority vote of the members present:

- Approval
    - Approved as submitted, no stipulations
    - Approved with stipulations; changes that are not substantive
    - Approved with stipulations; changes that are substantive
- Deferral
- Disapproval
- Withdrawal

Approval

The IRB may approve the protocol, ICF(s), and other study documentation as submitted (*i.e.*, without stipulation).

A *Notice of IRB Approval*, signed by the IRB Chair or designee that lists all of the ICF(s) and other study material(s) approved for use (*e.g.*, subject diaries, questionnaires, advertisements) will be provided to the PI. The PI may only begin advertisement, recruitment, screening, and enrollment upon receipt of the *Notice of IRB Approval* and finalization of any contracts.

The PI is responsible for forwarding a copy of the final protocol and any other materials to the applicable facility, sponsor, and/or funding agency, as required.

The approval of the convened IRB will be binding except that the Institution/IO may always disapprove a study that has been approved by the IRB; however, the converse is never true.

Review with Stipulations

The IRB may grant approval contingent on clarifications and/or revisions that are specifically detailed in a *Notice of IRB Comments* that is signed by the IRB Chair or designee. No research activities, including advertisement, recruitment, screening, or enrollment, may begin until all requisite stipulations have been satisfactorily addressed; this will be communicated to PIs in the written letter and through education initiatives.

At the convened IRB meeting, an assessment will be made whether the modifications/clarifications are substantive or not substantive in nature. Stipulations that are substantive will be those that seek information, clarification, or modification to the application that are directly relevant to the IRB's determination. Stipulations will not be considered substantive if revision to the information, clarification, or modifications can be specifically and clearly articulated at the meeting such that review of a PI's response/revised documents by the Chair, Vice Chair, or designated reviewer simply verifies the needed clarification or modification has been implemented by the PI.

If the IRB determines that the modifications/clarifications are substantive that finding will be documented in the minutes and PI's responses and corresponding revised documents will be presented to the convened IRB at a subsequent meeting to assess whether the modifications/clarifications are sufficient. Upon re-presentation to the convened IRB, the IRB will focus only on those issues that were deemed to be substantive in nature. The IRB's vote at the re-presentation will focus only on those issues presented.

If it is determined by the convened IRB that the stipulations/clarifications are not substantive in nature that finding will be documented in the minutes and the PI's responses and corresponding revised documents may be reviewed and verified via expedited review in the IRB office, provided the stipulations do not require deliberation by the convened IRB. The IRB Chair or designee may, at his/her discretion, opt to refer the PI's responses, *etc.*, to the convened IRB for consideration.

The PI's response should respond point by point to each stipulation. The responses should summarize the changes made and note which sections of the protocol, ICF, or supporting documents were changed in response. Tracked and untracked documents should be submitted. The tracked document should include only changes since the last submitted version.

Upon receipt of the PI's response to the IRB stipulations/request for clarification, an IRB staff member may conduct a pre-review of the submitted documents prior to review by the Chair or designee.

A letter signed by the PI addressing the stipulations/clarifications should accompany any revised documents. All documents should have a version date or number for ease of identification and document control.

Approval is conferred following verification that all IRB stipulations have been satisfactorily addressed. The *Notice of IRB Approval*, signed by the IRB Chair or designee that lists all of the ICF(s) and other study material(s) approved for use (e.g., subject diaries, questionnaires, advertisements) will be provided to the PI for use.

On a monthly basis the members of the IRB will be notified by the IRB Coordinator/Administrative Assistant of all items reviewed and approved via expedited review in the preceding month (*Notification to IRB of Documents Reviewed/Approved via Expedited Review Procedures* document*)*. Advertisement, recruitment, screening, and enrollment in a study may only begin upon receipt of the *Notice of IRB Approval* and the finalization of any contracts.

It is the responsibility of the PI to forward, as required, a copy of the final protocol and other IRB-approved materials to any applicable facility, sponsor, and/or funding agency.

The approval of the convened IRB will be binding except that the Institution/IO may always disapprove a study that has been approved by the IRB; however, the converse is never true.

The interval for the approval of any item presented to a convened IRB will be for 1 year, unless otherwise specified by the IRB taking into account the risk associated with study participation, *etc.*

Deferral

If the IRB determines that the information provided by the PI is not sufficient to complete a thorough review and render a determination[9], the study will be deferred. The reasons for deferral may include that the PI needs to clarify specific substantive issues, submit missing or significantly revised materials, and/or attend a meeting to participate in discussion and understanding of an aspect(s) of the research. The Primary Reviewer or the Chair will typically make a motion to defer a study; the motion will be voted on by the convened IRB.

The reason(s) for deferral will be recorded in the IRB meeting minutes.

If a study is deferred a *Notice of IRB Deferral* signed by the IRB Chair or designee will be provided to the PI, documenting the reason(s) for deferral and specifying the additional information or revisions required for re-presentation. Upon receipt of the requested information and/or revised documents, the IRB office staff and/or Chair and/or designee may first review the resubmission. If deemed acceptable to proceed, the PI's response, including attendant documents, will be scheduled for review at the next convened IRB meeting.

Disapproval

The IRB will disapprove any research that it determines to be unethical in nature. A *Notice of IRB Disapproval* letter signed by the Chair or designee will include a statement of the reasons for disapproval and give the PI an opportunity to respond in writing for reconsideration at a subsequent convened IRB meeting. The reason(s) for disapproval will be recorded in the IRB meeting minutes.

If a PI wishes to request IRB reconsideration, s/he may ask for formal reconsideration, as described in elsewhere in this manual.

Withdrawal

In the event that an application must be withdrawn from a meeting agenda the PI, the IRB Chair or designee, or the Primary Reviewer may withdraw a study from scheduled IRB review. Withdrawal may only be initiated before a study is presented at a convened IRB meeting. Reasons for withdrawal include a Primary Reviewer being unable to attend the meeting, new information learned too soon before the IRB meeting such that the members have not had sufficient time to review it, or the Primary Reviewer or Chair determine there are too many material issues that the PI has not responded to prior to the meeting.

7. Responses to IRB Reviews

Responses to IRB review comments/stipulations should be completed within three (3) months; otherwise, a new submission may be required, as determined by the IRB Chair or designee. This applies to all new research proposals and research presented for continuing review to ensure up-to-date scientific and safety-related information is included in the submission. Provisions will be made for extending the 3-month

[9] OHRP recommends that research be deferred if they require, "…substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the [IRB] determinations…" excerpt from OHRP Guidance on Written IRB Procedures, 01 July 2011

response time in the event that the PI justifies extenuating circumstances to the satisfaction of the IRB Chair or designee. The IRB Chair or designee will review such situations on a case-by-case basis and will render a decision.

If substantial stipulations potentially affecting subject safety are addressed at the time a modification to a previously approved study or a continuing review is reviewed by the convened IRB, the IRB may require a shorter response time. If so, this will be communicated in writing to the PI and will be documented in the minutes. Failure to respond to such review comment stipulations within the designated response time may result in the IRB suspending study activities.

In the normal course of review of a PI's response(s) to initial review, the IRB staff may conduct a preliminary review of responses and present his/her findings to the Chair or designee. The IRB Chair or the designee will review the submitted revisions to verify that they address the stipulations determined by the convened IRB. If the IRB Chair or designee deems the responses satisfactory, a *Notice of IRB Approval* will be forwarded to the PI or if previously indicated, the study will be forwarded to the IRB for reconsideration.

If the PI's response(s) are not satisfactory, the remaining requested revisions, clarifications, *etc.*, will be documented in the study file, and will be communicated to the PI either in writing or orally. Communication with the PI will be documented in the IRB study file.

8. Request for Reconsideration

A PI may request in writing the reconsideration of a decision made by the convened IRB concerning a study. The original Primary Reviewer will present the requested reconsideration at a convened IRB meeting. If the original Primary Reviewer is not available, the IRB Chair may either defer reconsideration until the original Primary Reviewer is available or appoint a different IRB member to present the reconsideration or may opt to present the reconsideration him/herself. Request for reconsideration may involve stipulations for approval, as well as voted actions (*e.g.*, disapproval). The decision of the convened IRB will be documented in the minutes and will be final; the decision will be sent to the PI in writing.

9. Creation of a Subcommittee

In the event of a tabled IRB deliberation and vote, or a deferral, or a request for reconsideration, or another reason deemed necessary by the convened IRB or Chair, the IRB may establish a subcommittee.

The Chair will appoint persons to the subcommittee and will specifically appoint a subcommittee Chair. Typically, a subcommittee will be composed of IRB members; however, persons at CHA who are not IRB members, or experts and consultants external to CHA, may be asked to meet with the subcommittee to discuss the research. The PI may also be invited to meet with the subcommittee or the convened IRB to address specific issues. The results of any subcommittee review, including recommendations, will be reported to the convened IRB when the issues are satisfactorily addressed.

The convened IRB will discuss the subcommittee recommendations and review any new submitted materials. The convened IRB may accept or reject the recommendation of the subcommittee. The decision of the convened IRB will be final except that the institution(s)/IO may always disapprove a study that has been approved by the IRB; however, the converse is never true. The PI will be informed of the final decision in writing.

10. Continuing Review[10, 11]

Continuing review will be conducted in accordance with Federal regulation.

Unless the IRB determines otherwise, continuing review of research is not required for research subject to the revised Common Rule in the following circumstances:

1. Research eligible for expedited review in accordance with 45 CFR 46.110;
2. Research reviewed by the IRB in accordance with limited IRB review;
3. Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
    a. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
    b. Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care

Note: In this manual "continuing review" is used as opposed to "progress report," which is also used in Federal regulation and guidance.

For protocols that are scheduled for continuing review, the IRB Coordinator/Administrative Assistant is expected to send a courtesy reminder to the PI two (2) months prior to expiration of IRB approval. Should a response to the initial courtesy reminder not be received, a second courtesy reminder should be sent by the IRB Coordinator/Administrative Assistant. Irrespective of the courtesy reminder, the PI is responsible for ensuring complete and accurate continuing review materials are submitted on time to avoid expiration of IRB approval.

If a PI does not submit the continuing review application by the dates outlined in the courtesy reminder(s) it may result in delay of IRB review of the research and may cause the IRB approval to lapse. If IRB approval lapses, then research-related activity may not take place. The PI may request in writing special consideration from the IRB Chair to continue to follow a research subject(s) in the event approval lapses (*e.g.*, subject's safety would be compromised by a lapse in research-related activity). The IRB Chair will consider such rare requests on a case-by-case basis. Any such limited permission will be documented in the IRB study file and will be conveyed to the PI in writing. The convened IRB will be notified if the Chair exercises this rare dispensation. In such a case, the PI will be required to expeditiously prepare and submit the requisite continuing review materials.

Continuing review must be substantive and meaningful.[12] The IRB will apply the same criteria for approval of continuing review as it does in the initial review (*i.e.*, acceptable risks, potential benefits, informed consent, safeguards for subjects). The same rules apply to continuing review as described previously for initial review. The concentration of the review may change within the approval year (*i.e.*, new Federal regulation or new Federal guidance or institutional policy or new study-specific information learned since the last IRB review);

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[10] FDA: Continuing Review After Study Approval – Information Sheet Guidance for IRBs and Clinical Investigators

[11] OHRP Guidance on Continuing Review, 10 November 2010

[12] Office for Human Research Protections Guidance on IRB Continuing Review of Research dated 10 November 2010

therefore, it is possible that revisions, enhancements, and/or clarifications of the study will be required at continuing review.

The frequency of continuing review will be at determined by the IRB and will be at intervals appropriate to the degree of risk, but not less often than once per year, as required by regulations. Depending upon the level of risk or other factors, such as inclusion of vulnerable populations, the safety monitoring plan, the presence of a DSMB, *etc.*, the IRB has the discretion to require continuing review on a more frequent basis. The IRB may, for example, require a PI to submit a progress report after enrollment of each subject, or prior to increasing dosage of a particular drug, or at specified time periods between continuing reviews, *etc.* The IRB minutes and the letter to the PI will specify the frequency of review.

If, in accordance with Federal regulation, continuing is not required, the IRB Coordinator/ Administrative Assistant will communicate with the PI on an annual basis coinciding with the approval date of the study to gather basic information such as a status update (e.g., study is active and ongoing or research activities have been completed and the study may be terminated), confirmation whether any SAEs have occurred and been reported to the IRB in the past year, a summary of any AEs that have occurred in the past year, annual COI disclosure information, the number/version date of the last amendment approved by the IRB, the current version date/number of the IRB-approved protocol, etc. In addition, the IRB Coordinator/Administrative Assistant will remind the PI of his/her responsibilities, including to report UPs and any problems, complaints, or subject injuries, and the PI's responsibility to ensure that each study team member has current research training certification in accordance with institutional policy. PIs will also be reminded of their responsibility to update the IRB in a timely manner regarding any status change related to the research (e.g., change in funding, change in enrollment status).

Exempt Research and Continuing Review

Research that is granted an exemption at the time of initial review will not be required to undergo continuing review; the exempt status of the research will not expire.

In proximity to the anniversary date of the granting of an exemption, the IRB Coordinator/Administrative Assistant will execute a similar process as that outlined above for minimal risk studies not required to undergo continuing review. The IRB Coordinator/Administrative Assistant will contact the PI to obtain basic information about the study, such as the status of the research (i.e., active or to be terminated), confirmation of current research education certification for all members of the study team, annual COI disclosure information for all members of the study team, and remind the PI of his/her continuing responsibilities, etc.

Expedited Continuing Review

In accordance with Federal regulations, some research may be reviewed and approved via expedited review procedures at the time of continuing review.[13, 14] A decision to use expedited review procedures will be made

[13] Categories of Research that May be Reviewed by an Institutional Review Board through an Expedited Review; Source: 63 FR 60364-60367, November 9, 1998.

[14] Office for Human Research Protections (OHRP) Guidance on IRB Continuing Review of Research dated 10 November 2010

by the IRB Chair or designee. Use of expedited review allows the IRB Chair or designee to exercise the authority of the convened IRB, therefore, not requiring the research to be presented to the convened IRB. However, the IRB Chair or designee may not use expedited review procedures to disapprove a study; such an action can only be taken by the convened IRB. The person who conducts the expedited review should document the applicable category for approval in the study file and it should be documented in the *Notice of IRB Approval – Continuing Review*.

Research that undergoes expedited continuing review is evaluated with the same regulatory criteria as research that is evaluated by the convened IRB.

Convened IRB Continuing Review

If a study is presented to the convened IRB for continuing review the IRB will review the current protocol, the ICF(s) that has been used to enroll subjects over the past year, and any proposed changes to the protocol and/or ICF to ensure accuracy and regulatory compliance. At the time of convened IRB continuing review, the convened IRB may make the determination that future continuing reviews may be performed by expedited procedures as permitted by Federal regulations.

Protocols for continuing review are reviewed and presented by a single reviewer. The reviewer of the continuing review will make a motion, another voting member of the IRB will second it, and the convened IRB will vote. The vote must be by a majority of members present constituting a quorum. All of the IRB actions referenced elsewhere in this manual may also be taken by the IRB for continuing review and follow parallel procedures as noted below.

As part of continuing review, the IRB may appoint 1 or more individuals (other than the PI) to observe the research or the consent process and report findings to the IRB. Among the reasons the IRB may appoint an observer:

- Enrollment of a vulnerable population in a greater than minimal risk study.
- Participants have limited decision making capacity.
- Multiple ICFs are employed in a study.
- Enrollment of healthy populations in a greater than minimal risk study, *e.g.*, early phase drug or device clinical trials.
- A short form ICF is used for non-English speaking participants.
- Consent is obtained orally.
- The study involves deception.
- Gene therapy research.
- Studies with prior non-compliance.

The IRB shall appoint such an individual whenever the IRB determines that monitoring is in the best interest of research subjects.

11. Quorum of the IRB

As described elsewhere in this document.

Deliberation and Voting Procedure

As described elsewhere in this document.

Preliminary Review

As described elsewhere in this document.

Primary Review

As described elsewhere in this document.

IRB Actions at Continuing Review

As described elsewhere in this document.

Reponses to IRB Continuing Review

As described elsewhere in this document.

Request for Reconsideration

As described elsewhere in this document.

Creation of a Subcommittee

As described elsewhere in this document.

12. Review of Modifications during Approval Period

For the purpose of this manual modification, amendment, addendum, revision, and change may be used interchangeably.

The IRB must approve any change to a study prior to the initiation of the change, even if the change reduces risk. Such changes may be reviewed and approved by expedited review or may require review and approval by the convened IRB.

The only exception to the requirement of obtaining IRB approval prior to initiating a protocol change is when a change is urgently necessary to eliminate apparent immediate hazards to a subject(s). Under such circumstances, the PI is to contact the IRB Chair, or the IRB office, immediately.

Expedited Review during the Approval Period

Whether a change may be reviewed and approved via expedited review or requires review by the convened IRB will depend whether the change is minor and involves minimal risk or is more than minor or greater than minimal risk, as defined by Federal regulations/guidance. Per Federal regulation[15] and guidance,[16] changes in previously approved research during the approval period may be reviewed and approved by expedited review procedures when appropriate. Only those changes that are minor or constitute minimal risk may be reviewed and approved via expedited review. The IRB Chair or designee will be responsible for determining whether or not the change is minor and whether or not the change is minimal risk or greater than minimal risk. In the event of a question, the IRB Chair will make any final decision.

Examples of minor changes in previously approved research that may be approved via expedited review in accordance with regulations generally include:

- Administrative changes,
- Changes falling into standard categories for expedited approval,
- Minor changes in requested enrollment numbers.

The IRB Chair or designee may forward a request for amendment to the convened IRB even if it qualifies for expedited review.

Form(s) and Process for Expedited Review during the Approval Period

If the PI wishes to amend a study or any research document during the course of the study, the proposed change(s) are to be submitted to the IRB in writing. The *Application for Research Modification to a Previously Approved Protocol* is to be completed, signed, and submitted to the IRB. The PI is responsible for identifying the requested changes (*e.g.*, tracked documents). All revised documents should have a version date or number for ease of identification and document control.

Upon receipt, an IRB staff member may conduct a pre-review of the submitted documents prior to IRB Chair or designee review. Upon review, the IRB Chair or designee may determine that the revisions present greater than minimal risk and/or are more than minor and should be reviewed by the convened IRB. In granting expedited approval, the reviewer should document the basis for the approval and any relevant findings.

If modification/clarification of the proposed change is required before expedited review and approval may be granted, the reviewer or an IRB staff member will communicate with the PI or a research team member. The communication may be written or oral and should be documented in the IRB study file.

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[15] 45 CFR 46.110; 21 CFR 56.110

[16] Office for Human Research Protections (OHRP) Guidance on the Use of Expedited Review Procedures dated 11 August 2003

Approval is communicated in the *Notice of Approval -- Expedited Review* and is typically signed by the reviewer; all study material(s) approved for use will be listed in the signed approval letter. On a monthly basis the IRB members will be notified of all items reviewed and approved via expedited review in the preceding month (*Notification to IRB of Documents Reviewed/Approved via Expedited Review Procedures* document*)*.

It is the responsibility of the PI, as necessary, to forward a copy of the final protocol and approved materials to the applicable facility, sponsor, and/or funding agency.

The approval will be final except that the Institution/IO may always disapprove a change to a study that has been approved by the IRB; however, the converse is never true.

Convened IRB Review during the Approval Period

If an amendment does not qualify for expedited review, or negatively affects the risk:benefit ratio, or is more than minor, or is greater than minimal risk, or is deemed to have an apparent effect on the risk:benefit ratio, the proposed change will be forwarded the convened IRB for review. A single reviewer will usually present the requested revision.

Quorum of the IRB

As described elsewhere in this document.

Deliberation and Voting Procedures

As described elsewhere in this document.

Preliminary Review

As described elsewhere in this document.

Primary Review

As described elsewhere in this document.

IRB Action at Convened IRB Review during the Approval Period

As described elsewhere in this document.

Responses to IRB Review

As described elsewhere in this document.

Request for Reconsideration

As described elsewhere in this document.

13. Reactivation of a Study

The PI may request reactivation of his/her previously terminated study. To reactivate it the PI should submit a signed written request to the IRB office, including a new study application. As needed, the IRB office staff will have any necessary archived materials recalled from off-site storage. Reactivation may occur via expedited review procedures, if appropriate; however, the IRB Chair or designee may opt to forward any request for reactivation to the convened IRB.

Reactivation of studies to enroll additional subjects, *etc.*, will be reviewed by the same procedures as the initial review (*e.g.*, expedited or convened IRB), provided that the study risk:benefit ratio has not been changed.

In the event that a study is terminated by a PI in error, the PI may reactive it by submitting a new study application to the IRB office explaining the circumstances under which the study was terminated. As described elsewhere in this manual, the study may be reactivated via expedited review procedures, if appropriate; however, the IRB Chair or designee may opt to forward any request to the convened IRB.

If IRB approval of a study lapses research-related activities may not take place, and may not resume, until the IRB has reviewed and re-approved the study.

14. Emergency Exemption from Prospective IRB Approval for Use of an Investigational Drug or Biologic[17]

Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)). The emergency use provision in FDA regulations (21 CFR 56.104(c)) is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

Life-threatening, for the purposes of section 56.102(d), includes the scope of both life-threatening and severely debilitating, as defined below.

- **Life-threatening** means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end

[17] FDA Guidance for Institutional Review Boards and Clinical Investigators 1998 Update; Emergency Use of an Investigational Drug or Biologic – Information Sheet

point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

- **Severely debilitating** means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

The physician should immediately contact the IRB office if s/he is seeking a one-time emergency use of an investigational drug or biologic (a "test article"). The IRB office will guide the physician and will contact the IRB Chair or designee to review the request. The Chair or designee may also be available by pager if the event occurs outside of normal business hours.

The IRB prefers written acknowledgment from the sponsor supplying the investigational drug or biologic be on file acknowledging the emergency use and noting agreement of the test article's use with the individual in question. The IRB recommends that the physician forward to the manufacturer a copy of the documentation sent to, and received from, the IRB regarding the emergency use.

Some manufacturers will agree to allow the use of a test article contingent on a letter from the IRB before the test article may be shipped. If it is not possible to convene an IRB meeting given the time parameters, the investigator is to submit to the IRB the following:

- Detailed information about the patient's condition, including a detailed letter addressing the person's medical history and current condition,
- Detailed information about the test article (*e.g.*, Investigator's Brochure),
- A protocol or other detailed document addressing test article administration/use, associated risks, monitoring plan, *etc.*,
- An ICF, and
- A letter from a clinician who not involved in the patient's care that confirms that standard care options have been exhausted.

After review and concurrence by the IRB Chair or designee, a written statement will be sent to the clinician stating that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). This, however, is not to be construed as "IRB approval."

The investigator is to report serious adverse events to the IRB.

Limits on Use of Data from Emergency Use under FDA Exemption

Regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subject. To be exempt from the requirement for IRB review for the emergency use of a test article in a life threatening situation, an investigator must not use the data in a systematic investigation designed to

develop or contribute to generalizable knowledge or else the exemption no longer applies. To comply with this limitation, investigators must follow these rules:

1. Do not use the emergency use exemption to circumvent the general requirement for prior IRB review;

2. Do not use data from an emergency use in a prospective research study; and

3. Do not report data from an emergency use in a retrospective research study, unless granted specific approval by the FDA and IRB.

When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity.

The Informed Consent Process in an Emergency Use Situation[18, 19]

If a patient's medical condition is stable the investigator is to develop an ICF that the individual will be asked to read and sign. In some circumstance, the sponsor/test article manufacturer may provide an ICF for use. The ICF must explain the investigatory nature of the test article, as well as potential risks and benefits. If time permits, the IRB Chair should first review the ICF. A copy of the signed ICF is to be given to the subject, and a copy of the ICF should be placed in the patient's medical record.

If the physician determines that the subject is not capable of understanding the proposed intervention and cannot sign the ICF, a health care proxy, if one was designated, or a LAR is to be approached to provide permission. Absent a designated health care proxy, the next-of-kin is to be approached for permission. The recognized priority of the next-of-kin relationship for research follows the clinical hierarchy:

1. Spouse
2. Adult children
3. Parent
4. Adult siblings

[18] FDA Guidance for Institutional Review Boards and Clinical Investigators 1998 Update; Drugs and Biologics

[19] OPRR Reports: Informed Consent Requirements in Emergency Research, 31 October 1996; OHRP Informed Consent FAQs

Exception from Informed Consent Requirement in Emergency Use Situation[20]

Even for an emergency use, the investigator is required to obtain informed consent from the patient or permission from the patient's LAR, unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following (21 CFR 50.23(a)):

1. The patient is confronted by a life-threatening situation necessitating the use of the test article.

   > Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the patient.

3. Time is not sufficient to obtain permission from the patient's LAR.

4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the patient's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the patient's life, and if time is not sufficient to obtain an independent physician's determination that the four (4) conditions above apply, the clinician should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The clinician must notify the IRB within 5 working days after the use of the test article (21 CFR 50.23(c)), as discussed elsewhere in this manual.

The IRB Chair will review the notification to ensure that the emergency use meets the applicable regulations. The physician is advised that if s/he anticipates the need to use the investigational article in additional persons, review and approval by the convened IRB is required.

Exception from Informed Consent for Studies Conducted in Emergency Settings

When research will be conducted in an emergency setting, *e.g.*, testing a blood substitute in the field, waiver of prospective subject consent is allowed in accordance with 21 CFR 50.24. Such research protocols must be approved in advance by the FDA and the IRB, and public disclosure must be made to the community in which the research will be conducted. Such studies are different from the emergency use of an investigational test article and usually are not eligible for the emergency approvals described above.

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[20] FDA Guidance for Institutional Review Boards and Clinical Investigators 1998 Update; Exception from Informed Consent for Studies Conducted in Emergency Settings" Regulatory Language and Excerpts from Preamble

For this type of research, the IRB would be guided by the guidance document "*Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble*,"[21] which is a compilation of the wording of 21 CFR 50.24 and pertinent portions of the preamble from the 02 October 1996 Federal Register.

Emergency IND Number

The need to use an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND application. The FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by the clinician by telephone or other means of rapid communication (21 CFR 312.36).

The researcher should consult the FDA directory for contact information related to obtaining an Emergency IND.

15. Off-label Use and Investigational Use of Marketed Drugs, Biologics, and Medical Devices[22]

Good medical practice and the best interests of a patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgment. If a physician uses a product for an indication not in the FDA-approved labeling, s/he is responsible to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an IND, IDE, or review by the IRB.

Investigational Use of Marketed Drugs, Biologics and Medical Devices[23]

The investigational use of approved, marketed products is different from the situation described above. "Investigational use" suggests the use of an approved product in the context of a clinical study protocol (see 21 CFR 312.3(b)). IRB review is required for studies involving investigational use of marketed drugs, biologics, *etc.*, regardless of whether an IND is required.

When the intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND or IDE may be required; however, per 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all 6 of the following conditions are met:

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[21] Exception from Informed Consent For Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble

[22] Guidance for Institutional Review Boards and Clinical Investigators 1998 Update; "Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices

[23] FDA Frequently Asked Questions About Therapeutic Biological Products

1. It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
2. It is not intended to support a significant change in the advertising for the product;
3. It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. It is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);
5. It is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7); and
6. It does not intend to invoke 21 CFR 50.24.

Investigators are to refer to the FDA website or directory for contact information to help them determine whether or not an IND or IDE is required in a specific situation.

Investigational Drugs [24, 25]

With applicable IRB review and approval, investigational products may be used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The mechanisms outlined below expand access to therapeutic agents without compromising the protection afforded to subjects or the thoroughness and scientific integrity of product development and marketing approval.

Expanded Access of Investigational Drugs

Expanded access is the use outside of a clinical trial of an investigational medical product (*i.e.*, one that has not been approved by FDA).

Per the FDA, wherever possible, use of an investigational medical product by a patient as part of a clinical trial is preferable because clinical trials can generate data that may lead to the approval of products and, consequently, to wider availability. However, when patient enrollment in a clinical trial is not possible (e.g., a patient is not eligible for any ongoing clinical trials, or there are no ongoing clinical trials), patients may be able to receive the product, when appropriate, through expanded access.

21 CFR part 312 subpart I provides general requirements, describes criteria that must be met to authorize expanded access, lists requirements for expanded access submissions, and describes safeguards that will protect patients and preserve the ability to develop meaningful data about the use of the investigational product.

Under FDA's regulations for investigational drugs and biologics, there are three categories of expanded access:

- Expanded access for individual patients, including for emergency use;

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[24] FDA Information Sheet Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

[25] FDA Treatment Use of Investigational Drugs – Information Sheet

- Expanded access for intermediate-size patient populations; and
- Expanded access for widespread use.

Open Label Protocol or Open Protocol IND

These are usually uncontrolled studies conducted to obtain additional safety data (Phase III studies). They are typically used when the controlled trial has ended and intervention is continued so that subjects and controls may continue to receive the benefits of the investigational drug until marketing approval is determined. In accordance with FDA guidelines, these studies require prospective IRB review and informed consent must be obtained from study participants. Investigators must complete an application for initial review, which must be approved by the convened IRB as outlined elsewhere in this manual.

Treatment IND

A treatment IND (21 CFR 312.34 and 312.35) is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted by the FDA after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks.

There are 4 requirements that must be met before a treatment IND can be issued:

1. The drug is intended to treat a serious or immediately life-threatening disease;
2. There is no satisfactory alternative treatment available;
3. The drug is already under investigation, or trials have been completed; and
4. The study sponsor is actively pursuing marketing approval.

In accordance with FDA guidance, treatment IND studies require prospective IRB review and informed consent from study participants. A sponsor may apply to the FDA for a waiver of local IRB review under a treatment IND if it can be shown to be in the best interest of the subjects, and if a satisfactory alternative mechanism for assuring the protection of subjects is available, *e.g.*, review by a central IRB. Such a waiver does not apply to the informed consent requirement. The IRB may still opt to review a study even if the FDA has granted a waiver. On a protocol-by-protocol basis the IRB will assess whether IRB review of the ICF is needed. If the FDA has not granted a waiver, the investigator must submit an initial review application, which must be reviewed and approved by the convened IRB.

Group C Treatment IND

The "Group C" treatment IND was established by agreement between FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial.

Group C drugs are usually Phase III study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. Properly trained physicians can generally administer them without the need for specialized supportive care facilities. Group C drugs are distributed only by the NIH under NCI protocols. Although treatment is the primary objective and patients treated under Group C guidelines are not part of a clinical study, safety and effectiveness data are collected. Because administration of Group C drugs is not

done with research intent, the FDA has generally granted a waiver from IRB review requirements (21 CFR 56.105).

Even though FDA has granted a waiver for these drugs, an IRB may still choose to conduct a review under its policies and procedures. The usage of a Group C drug is described in its accompanying "Guideline Protocol" document. The Guideline Protocol contains a FDA-approved ICF that must be used if there has been no local IRB review.[26] On a protocol-by-protocol basis the IRB will determine the need for the IRB to review use of investigational agents with Group C Treatment INDs.

Parallel Track

The FDA's Parallel Track policy (57 FR 13250) permits wider access to promising new drugs for AIDS/HIV related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating AIDS/HIV. Such studies require prospective IRB review and subject informed consent. Investigators must submit a complete initial review application, which must be reviewed and approved by the convened IRB.

Emergency Use IND

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In such cases, FDA may authorize shipment of the drug for a specified use (21 CFR 312.36). Such authorization is usually conditioned upon the sponsor/manufacturer filing an appropriate application as soon as practicable. Prospective IRB review is required unless the conditions for exemption are met (21 CFR 56.104(c) and 56.102(d)). Informed consent is required unless the conditions for exception are met (21 CFR 50.23). The procedures in the sections of this manual addressing new study applications and emergency exemption from IRB approval will be followed, as applicable.

Expanded Access of Investigational Devices

Typically, investigational devices with significant risks may only be used on human subjects after IRB review and approval through an FDA-approved clinical trial for which an investigational device exemption (IDE) allows the investigational device to be used in a clinical study. However, there are circumstances under which a health care provider may use an investigational device outside of a clinical study to save the life of a patient or to help a patient suffering from a serious disease or condition for which no other alternative therapy exists.

If enrollment in an existing IRB-approved clinical trial is not possible (*e.g.*, a patient is not eligible for any ongoing clinical trials, or there are no ongoing clinical trials to address the patient's condition), patients/physicians have the potential to receive expanded access to investigational devices under one of three alternative mechanisms.

- Emergency Use
- Compassionate Use (or Individual Patient/Small Group Access)

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[26] National Cancer Institute Investigator's Handbook

- Treatment Use

16. Medical Devices[27, 28, 29]

FDA defines a medical device, in part, as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, toothpastes, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for *in vitro* diagnosis (IVD) of disease and other medical conditions, such as pregnancy.

Clinical investigations of medical devices must comply with FDA informed consent and IRB regulations (21 CFR parts 50 and 56, respectively). Except for certain low risk devices, each manufacturer seeking to introduce a new medical device to the market must submit a pre-market notification to FDA. FDA reviews the notifications to determine if the device is "substantially equivalent" to a device that was marketed prior to passage of the Amendments (*i.e.*, a "pre-amendments device").

If the new device is deemed "substantially equivalent" to a pre-amendments device (a "predicate device"), it may be marketed immediately and is regulated in the same regulatory class as the pre-amendments device to which it is equivalent. The pre-market notification requirement for new devices and devices that are significant modifications of already marketed devices is described in section 510(k) of the Federal Food, Drug, and Cosmetic Act. Devices determined by FDA to be "substantially equivalent" are often referred to as "510(k) devices."

If the new device is not deemed to be substantially equivalent to a pre-amendments device, it must undergo clinical testing and pre-market approval before it can be marketed unless it is reclassified into a lower regulatory class.

Investigational Device Exemption (IDE)[30]

An investigational device is a medical device that is the subject of a study designed to evaluate the effectiveness and/or safety of the device. Studies undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the IDE regulations (21 CFR 812).

Certain clinical investigations of devices (*e.g.*, certain studies of lawfully marketed devices) may be exempt from the IDE regulations (21 CFR 812.2(c)).

Unless exempt from the IDE regulations, an investigational device is categorized as either "significant risk" (SR) or "non-significant risk" (NSR).

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[27] Information Sheet Guidance of IRBs, clinical Investigators, and Sponsors – Frequently Asked Questions About Medical Devices, January 2006

[28] Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors

[29] Device Advice: Device Regulation and Guidance

[30] 21 CFR 812

The study may not commence until FDA has approved the IDE application and the IRB has approved the study.

In contrast, NSR device studies do not require submission of an IDE application to FDA. Instead, the sponsor is required to conduct the study in accordance with the "abbreviated requirements" of the IDE regulations (21 CFR 812.2(b)).

Unless otherwise notified by FDA, a NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements. The abbreviated requirements address, among other things, the requirements for IRB approval and informed consent, recordkeeping, labeling, promotion, and study monitoring. NSR studies may commence immediately following IRB approval. The PI or the study sponsor, as applicable, is responsible to ensure that the abbreviated requirements are satisfied for a study.

Additional information about IDE policies and procedures are available on the FDA website.[31]

IRB Review of the Protocol and Informed Consent

Once a SR/NSR decision is rendered by the IRB or FDA, the IRB must consider whether or not the study should be approved. In considering whether a study should be approved, the IRB will use the same criteria it would use in considering approval of any research involving an FDA regulated product (21 CFR 56.111). The PI is to submit a complete application for initial review, as described elsewhere in this manual. The application is to include the necessary IRB forms and a copy of the Investigator's Brochure or equivalent supporting materials, and information necessary for the SR/NSR determination as outlined elsewhere in this manual.

Some NSR studies may also qualify as "minimal risk" studies and may be reviewed through an expedited review procedure (21 CFR 56.110).

FDA considers all SR studies to present more than minimal risk; convened IRB review is required. During review the IRB will consider the risks and benefits associated with the device compared to the risks and benefits of alternative devices or procedures. Procedures for initial approval, continuing review, and amendment are the same as for other studies and are detailed elsewhere in this manual.

Significant Risk and Non-significant Risk Medical Device Studies[32]

IDE regulations (21 CFR 812) describe 2 types of device studies, SR and NSR.

A SR device study is defined (21 CFR 812.3(m)) as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or

[31] FDA Guidance on IDE Policies and Procedures, 20 January 1998

[32] Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors – Significant Risk and Nonsignificant Risk Medical Device Studies, January 2006

- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

A NSR device study is one that does not meet the definition for a significant risk study.

NSR device studies, however, should not be confused with the concept of "minimal risk," a term used to identify certain studies that may be approved through an expedited review procedure.

For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study (21 CFR 50).

SR device studies must follow all the IDE regulations at 21 CFR 812. SR device studies must have a FA-approved IDE application before they may proceed. NSR device studies do not have to have an IDE application approved by the FDA, and may start at the institution as soon as the IRB reviews and approves the study and without prior approval by the FDA.

A NSR/SR Decision[33, 34]

The PI presents the initial determination to the IRB. This determination may be from the sponsor, or have been previously made by the FDA. The IRB will review the sponsor's SR or NSR determination for an investigational medical device study reviewed. If the FDA has already made a determination, that determination will be final; however, the IRB reserves the right to apply protections commensurate with its own assessment of the device and the protocol's risk, even if the FDA has determined a device to be NSR.

The PI must provide the IRB with a description of the device, any reports of prior investigations/studies involving the device, the proposed investigational plan, a description of subject selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The PI should inform the IRB whether any other IRB(s) has reviewed the proposed study and what determination(s) was made.

For a SR device, or NSR device with an IDE, the convened IRB will make the determination. A NSR device without an IDE may have the determination made by the IRB Chair or designee. When a SR/NSR decision is made by the convened IRB it will be documented in the IRB meeting minutes. When made by the expedited reviewer, the determination will be documented as part of the review.

In making the determination, the IRB will consider the submitted information, the above definition(s), and the prior determination pertaining to similar devices. In deciding if a study poses a SR, the IRB may consider the

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[33] Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors – Significant Risk and Nonsignificant Risk Medical Device Studies, January 2006

[34] Presentation: Institutional Review Board responsibilities in Making the Significant Risk and Non-significant Risk Device Determination

basis for the risk, including the proposed use of the device, the nature of the harm that may result from use of the device, and any additional procedures and any potential harm it may cause. Studies where the potential harm to subjects could be life threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure will be considered SR. Also, if a subject must undergo a procedure as part of the investigational study, *e.g.*, a surgical procedure, the IRB will consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

The IRB may engage outside consultants as necessary, or consult the FDA in making the determination.[35]

The IRB may agree or disagree with a sponsor's initial NSR assessment. If the IRB agrees with a sponsor's initial NSR assessment and approves the study, per FDA, the study may begin without submission of an IDE application to FDA. If the IRB disagrees and determines the device is SR, the sponsor should notify FDA that a SR determination has been made. The study may be conducted as a SR investigation following FDA approval of an IDE application.

Emergency Use of Unapproved Medical Devices[36,37,3839]

In accordance with FDA guidance, an unapproved medical device is defined as a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for pre-market approval under section 515 of the Federal Food, Drug, and Cosmetic Act (FD & C Act, 21 U.S.C. 360(e)). Medical devices that have not received marketing clearance under section 510(k) of the FD & C Act are also considered unapproved devices.

An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved IDE application under section 520(g) of the FD & C Act (21 U.S.C. 360(j), (g)) and 21 CFR part 812.

The FDA acknowledges that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to FDA that an emergency need actually existed. The IRB applies the

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[35] Procedures for Handling Inquiries Regarding the Need for an Investigational Device Exemptions Application for Research Involving Medical Devices, October 26, 2001

[36] Guidance for Institutional Review Boards and Clinical Investigators 1998 Update; Medical Devices

[37] Emergency Use of Unapproved Medical Devices

[38] FDA Guidance - Emergency Use Authorization of Medical Products July 2007

[39] "Off-label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices – Information Sheet Guidance for Institutional Review Boards and Clinical Investigators

procedures for emergency exemption from IRB approval described for drugs and biologics described elsewhere in this manual to unapproved medical devices.

Requirements for Emergency Use of a Device

Each of the following conditions must exist to justify emergency use of an investigational device:

1. The patient is in a life-threatening condition that needs immediate treatment;
2. No generally acceptable alternative for treating the patient is available; and
3. Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. Similar to the information elsewhere in this manual related to the emergency use of unapproved drugs or biologics, the IRB prefers to be notified in advance of such use.

A physician may not conclude that an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physicians should be aware that the FDA and the IRB expect them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures sufficiently in advance to avoid creating a situation in which such arrangements are impracticable.

In the event that a device is to be used in circumstances meeting the criteria listed above, the device developer should notify the Center for Devices and Radiological Health (CDRH), Program Operation Staff by telephone immediately after shipment is made. Note: an unapproved device may not be shipped in anticipation of an emergency.

FDA expects a physician to follow as many subject protection procedures as possible. These include:

- Obtaining an independent assessment by an uninvolved physician;
- Obtaining informed consent from the patient or his/her LAR;
- Notifying the IRB;
- Notifying the CHA IO as specified by institutional policies; and
- Obtaining authorization from the IDE holder, if an approved IDE for the device exists.

The IRB prefers notification in advance of the use. As for unapproved drugs and devices, the IRB will give priority to ensuring that proposed emergency uses are forwarded to the next convened IRB meeting. If the use can be safely delayed until the convened meeting, the PI should submit the proposed ICF, independent assessment by an uninvolved physician, device information including IDE information, and other relevant supporting materials to the IRB for review at the convened meeting. If the use must occur prior to the convened meeting, the same materials should be submitted to the IRB office for review by the office staff and IRB Chair or designate. Procedures for review are as presented elsewhere in this manual.

After-use Procedures

After an unapproved device is used in an emergency, the physician is to:

- Report to the IRB within 5 business days (21 CFR 56.104(c)) and otherwise comply with provisions of the IRB regulations (21 CFR part 56);

- Evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and a FDA-approved IDE for the device's subsequent use; and

- If an IDE for the use does exist, notify the sponsor of the emergency use, or if an IDE does not exist, notify FDA of the emergency use (CDRH Program Operation Staff) and provide FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results.

Subsequent emergency use of the device may not occur unless the physician or another person obtains FDA IDE approval for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist. Developers of devices that could be used in emergencies should anticipate the likelihood of emergency use and should obtain an approved IDE for such uses.

Limits on Use of Data in Emergency Device Use Situations

As described elsewhere in this document.

Informed Consent Process in Emergency Use Device Situations

As described elsewhere in this document.

Exception from Informed Consent Requirement

As described elsewhere in this document.

Exception from Informed Consent for Planned Emergency Research

As described elsewhere in this document.

Evening/Weekend Emergency Use for Treatment of a Patient with an Investigational Test Article

During evening hours, weekends, or holidays, the IRB Chair may be available by pager. If it is determined by an attending physician that the use of investigational therapy must not be delayed until normal business hours, and the IRB Chair is not available, the attending physician may proceed with the emergency investigational intervention for the specific patient in accord with FDA regulations and as described elsewhere in this manual.

17. Humanitarian Use Device (HUD)[40, 41, 42]

In accordance with Section 3052 of the 21st Century Cures Act (Pub. L. No. 114-255, https://www.congress.gov/114/bills/hr34/BILLS-114hr34eah.pdf) a HUD is a medical device that is intended to benefit patients in the treatment or diagnosis of a disease or condition that affect or is manifested in not more than 8,000 individuals in the United States per year.

The Office of Orphan Products Development (OOPD) determines if a device meets specific requirements, including scientific rationale and population prevalence, for designation as a HUD.

A Humanitarian Device Exemption (HDE)[43] application is similar to a pre-market approval, but because a HUD is exempt from the effectiveness requirements of a pre-market approval, a HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. However, the HDE must contain sufficient information for FDA to determine that the probable benefit to health outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment (section 520(m)(2)(c)). An approved HDE authorizes marketing of a HUD.

A HUD should be administered only if such use has been approved by the IRB. HUDs should not be used until after the HDE applicant obtains approval of the HDE from FDA and the IRB approves its use. The IRB will ensure that HDE approval has been granted before approving the device for use at CHA.

Initial Review of a HDE

Initial IRB approval will be performed at a convened IRB meeting. The IRB does not need to review and approve individual uses of a HUD, but the IRB may approve use of a HUD without any further restrictions, under a protocol, or on a case-by-case basis. The PI is to submit an initial review application as outlined elsewhere in this manual.

Continuing Review of a HDE

The IRB may approve the use of the device for a period of time, not to exceed 1 year. Based on the level of risk the IRB may approve a HUD for a specific number of patients and require a summary report before approving the use in additional patients. This will be assessed on a case-by-case basis and will be documented in the IRB meeting minutes.

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[40] FDA regulations; 21 CFR 814, subpart H, Humanitarian Use Devices

[41] Guidance for DHE Holders, Institutional Review Boards, Clinical Investigators, and FDA Staff – Humanitarian Device Exemption Regulations: Questions and Answers, 08 July 2010

[42] FDA website, Designating Humanitarian Use Device (HUD), https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/designatinghumanitarianusedeviceshuds/default.htm

[43] Humanitarian Device Exemption Overview

Continuing review should follow the requirements found at 21 CFR 56, and may be conducted using the expedited review procedures (see 21 CFR 56.110) unless the IRB determines that convened IRB review should be performed. A finding whether expedited continuing review is acceptable will be made by the convened IRB and documented in the IRB meeting minutes.

Informed Consent with a HUD

Federal regulations do not require informed consent from an individual for use of a HUD. Because a HDE provides for marketing approval, use of the HUD does not constitute research or an investigation that would normally require consent from a study subject.

However, the CHA IRB requires prospective informed consent, when feasible. Materials developed by the PI or previously developed by the HDE holder that incorporate information that may be used to assist a patient in making an informed decision about the use of the device should be submitted for IRB review. The informed consent process must clearly communicate the potential risks and benefits associated with the HUD, as well as any procedures associated with the use of the device and alternatives to the use of the device. It must also state that the device is a HUD for which effectiveness for the labeled indication has not been demonstrated, and explain the nature of HUDs (see 21 CFR 814.104(b)(4)(ii)).

Unless it is an emergency, before a HUD is used off-label, the IRB requires following the FDA recommendation that the HDE holder obtain FDA approval of the use following the compassionate use policy for unapproved devices.[44] If the FDA approves the compassionate use request, the physician must ensure that patient protection measures are addressed before the device is used and should devise an appropriate schedule for monitoring the patient. If the situation is life threatening and there is not sufficient time to obtain FDA approval for the off-label use, FDA recommendations in the relevant guidance must be followed and IRB procedures outlined elsewhere in this manual regarding emergency uses are to be followed.

Sometimes a physician or HDE holder may develop a research protocol designed to collect safety and effectiveness data to support a pre-market approval for the device. In such a case, an IDE is not required if the research is within the approved labeling; however, IRB approval of the study must be obtained before the research may begin. Informed consent must also be obtained from subjects participating in the study. If the research is for a new use, IDE regulations must be followed (21 CFR 812, 50, and 56).

18. Unanticipated Problem and Adverse Event Reporting[45, 46]

Adverse event reporting to the Institutional Review Board (IRB) and, in some circumstances, Federal agencies, is required by Federal regulation. Both Federal policy (Common Rule) [45 CFR 46 and US

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[44] See Chapter III Expanded Access to Unapproved Devices of the IDE Policies and Procedures Guidance Pre-Market Approval, 20 January 1998

[45] OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse events, January 15, 2007

[46] FDA Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs- Improving Human Subject Protections, January 2009

Food and Drug Administration regulations [21 CFR 56.108(b)(1); 21 CFR 312.66] require the reporting of unanticipated problems involving risks to study participants or others to the IRB and appropriate institutional officials.

Please refer to CHA policy A-COM-0007 (Reporting to the IRB of Adverse Events and Unanticipated Problems Involving Risks to Study Participants or Others) for details of this policy, including applicability, definitions, procedures, etc.

19. Record-keeping Requirements

IRB Record-keeping Requirements

The IRB Coordinator/Administrative Assistant maintains study-specific records of the IRB's activities for 7 years after completion of the research. This policy is in accordance with Federal regulations and the Massachusetts General Laws guiding contract and tort claim (MGL Chapter 260 §2 and 2A).

For the purposes of this manual, completion of research is defined as the time when the PI notifies the IRB that a study is to be terminated. Termination is defined as the time when all research-related activity has concluded, including subject intervention, follow-up, data queries, *etc.*

IRB records (active and terminated) are available for inspection and copy by the FDA, authorized Federal or state government agencies, institutional compliance auditors, or hospital accrediting agencies (*e.g.*, Joint Commission on Accreditation of Healthcare Organizations) in the course of carrying out their respective duties.

The following records are also maintained:

- IRB membership rosters for 5 years;
- Written policies and procedures, forms and other instructions;
- Minutes of meetings for 7 years upon termination of a study.
- For each study reviewed by the IRB, a copy of the initial submission (application forms, proposed protocol and ICF(s)), together with, but not limited to, the following items as applicable will be retained:
    - Notification letters to a PI regarding IRB actions
    - Approved protocol(s)
    - Approved ICF(s)
    - Amendment request(s)
    - SAE reports
    - Unanticipated event reports
    - Continuing Review applications, as applicable
    - HIPAA-related documents
    - Investigator's Brochure(s), PDR excerpts, MSDS Sheets, relevant scientific articles, *etc.*
    - All correspondence received by/sent to/from the IRB office

- All written information containing materials provided to subjects including, but not limited to, telephone scripts, interview text, questionnaire(s), survey instrument(s), advertisement(s), contact letter(s), *etc.*

- A copy of the IRB meeting agenda provided to IRB members at an IRB meeting will be retained for 3 years.

PI Record-keeping Requirements

Sponsored Research

A PI is responsible for maintaining research records as agreed to in a clinical trial agreement with a sponsor, or as otherwise directed and documented by CHA Office of Sponsored Research per policy.

Investigational Drugs

In accordance with 21 CFR 312.57(c), a PI or sponsor is to retain the records and reports required by Subpart D of the section for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.[47]

Investigational Devices

In accordance with 21 CFR 812.140, a PI or sponsor is to maintain the records required by Subpart G of the section during the investigation and for a period of 2 years after the latter of the following 2 dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a pre-market approval application or a notice of completion of a product development protocol.[48]

Other

The PI of a study that does not have a clinical trial agreement, or is not regulated by the FDA, is required to maintain research records for 7 years after s/he has terminated the study with the IRB.

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[47] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm

[48] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm

20. Accessing IRB Files

Upon request, a PI and/or research team members will be permitted access to those IRB study files in which they have a participating role. Access will be under the supervision of the IRB office staff. A PI may authorize a study team member to access the IRB study file by providing written authorization to the IRB office. It will be the practice of the IRB office to document access to the IRB study file by any member of the research team. The written authorization from the PI will be retained in the IRB file.

Members of the Office of Research Administration and other internal offices with a legitimate need may access relevant IRB files, as needed, with the written permission of the Chief Compliance Officer.

Only materials submitted by the research team and official correspondence from the IRB to a PI may be photocopied by any of the above-cited parties. Any IRB review(s) or intra-office communications (*e.g.* Memoranda or Note to File) may not be photocopied without the written and signed authorization of the IRB Chair. IRB meeting minutes may not be copied or accessed by the study team.

An IRB member may access the IRB study file(s) in the course of conducting an assigned review.

All IRB staff, including the IO and the Chair, will have access to all IRB study files. In the event that proceedings require restricted access, the IO or his/her designee will maintain such documents.

21. IRB Reviewer Contact with Study Sponsors [49]

When conducting the review of a protocol, an IRB Reviewer should never directly communicate with a study sponsor; all contact with the study sponsor is to be conducted by the PI. If an IRB reviewer seeks information from a sponsor, s/he is to discuss the matter with the PI, who may opt to contact the sponsor. The PI may choose to contact the sponsor with the IRB reviewer present (*e.g.*, present and possibly on speakerphone for a conversation); however, this is at the discretion of the PI.

C. Special Considerations

This section discusses topics that require special IRB consideration, including:

- Informed Consent
- Waiver of Consent
- Short Form Use
- Translation of Study Documents
- Vulnerable Populations

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[49] FDA: Sponsor-Investigator-IRB Interrelationship – Information Sheet Guidance for IRBs and Clinical Investigators

- International Research
- Ionizing Radiation

  Massachusetts Controlled Substances Registration

  IRB Administrative Fee
- Certificate of Confidentiality
- Subject Complaints
- Non-compliance
- Involuntary Suspension and Termination
- Education Requirements
- HIPAA

1. Informed Consent[50, 51, 52, 53, 54]

Please refer to CHA policy A-COM-0004 (Informed Consent for Research and Authorization for the Use and Disclosure of Protected Health Information) for details of this policy, including applicability, definitions, procedures, etc., and criteria for waiver or alterations of informed consent.

Research involving human subjects is subject to Federal regulations (45 CFR 46, 21 CFR 50) governing informed consent. The IRB considers informed consent a dynamic process. An ongoing dialogue should take place between the PI/research team and the (prospective) subject/the LAR/parent/guardian, hereafter referred to as the subject, concerning the research; this should occur throughout a subject's participation in a research study. The ICF, which formalizes and documents the discussion about the research, must be signed unless the IRB either granted a waiver of informed consent or a waiver of written documentation of informed consent.

Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the

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[50] FDA: A Guide to Informed Consent – Information Sheet Guidance for IRBs and Clinical Investigators

[51] OHRP Tips on Informed Consent

[52] OHRP "Exculpatory Language in Informed Consent," Cooperative Oncology Group Chairpersons Meeting 15 November 1996

[53] FDA: IRB Frequently Asked Questions – Information Sheet Guidance for IRBs and Clinical Investigators

[54] OHRP Policy and Guidance: Informed Consent

prospective subject's or LAR's understanding of the reasons why one might or might not want to participate. The IRB considers the ICF documentation of the dialogue and consent process that must occur between the PI, or his/her representative, and the prospective subject. However, the ICF, is not a substitute for discussion with prospective or enrolled subjects.

The ICF should be concise and it should not contain grammatical or spelling errors. It should be worded in the second person and should be written at approximately a 7th grade reading level, or as appropriate to the reading level and comprehension of the subjects. Technical or medical terms and jargon are to be avoided or explained. The ICF may not be coercive or contain exculpatory language through which the subject or the LAR is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence. Informed consent must also be obtained for subject eligibility screening. If a separate ICF is used for screening, it must also include a brief description of the full study, as necessary for a subject to determine if s/he wants to participate in screening.[55] Investigators may prospectively request a waiver or alteration of the consent process for screening; however, waiver will only be granted if the research activities meet the criteria specified in the relevant regulations.

Only an IRB-approved ICF(s) may be used to enroll subjects.

While the Common Rule provides for some subject confidentiality protections, the HIPAA Privacy Rule adds substantially greater privacy protections for human subjects and establishes the conditions under which protected health information (PHI) may be used or disclosed by CHA for research purposes. CHA policy with respect to human subjects involved in research is subject to Federal regulation and with respect to the use or disclosure of PHI for research purposes may be found in CHA policy A-COM-0004 (Informed Consent for Research and Authorization for the Use and Disclosure of Protected Health Information).

Informed Consent Process

Please refer to CHA policy A-COM-0004 (Informed Consent for Research and Authorization for the Use and Disclosure of Protected Health Information) for complete details on the informed consent process, etc.

Informed consent is the process by which information is presented to an individual to enable the individual to voluntarily decide whether or not to participate as a research subject.

Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

The PI must provide a prospective subject or the LAR with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information. A subject or his/her LAR is to have adequate opportunity to read the ICF, ask questions and obtain answers, and discuss and consider whether or not to participate in the study or not. The information that is given to the subject or the LAR shall be in

[55] FDA: Screening Tests Prior to Study Enrollment – Information Sheet Guidance for IRBs and Clinical Investigators

language understandable to the subject or the LAR. The consent discussion is to minimize the possibility of coercion or undue influence and should occur in a private, quiet location. A written copy of the ICF is to be given to the person signing the ICF.

Investigators are strongly encouraged to record a memorandum or note to file to document the consent/assent process. Information in such documentation would typically include information about those present during the consent/assent discussion, the nature of the issues discussed, a summary of questions asked by the prospective subject or his/her LAR and the research team members' responses, the location of the consent discussion, etc.

At the time of initial review, the IRB may appoint 1 or more individuals (other than the PI) to observe the research or the consent process and report findings to the IRB. Among the reasons the IRB may appoint an observer:

- Enrollment of a vulnerable population in a greater than minimal risk study.
- Participants have limited decision making capacity.
- Multiple ICFs are employed in a study.
- Enrollment of healthy populations in a greater than minimal risk study, *e.g.*, early phase drug or device clinical trials.
- A short form ICF is used for non-English speaking participants.
- Consent is obtained orally.
- The study involves deception.
- Gene therapy research.

The IRB shall appoint such an individual whenever the IRB determines that monitoring is in the best interest of research subjects.

Based on the nature of the study, a PI may be required to obtain and document the consent of a participant on more than one occasion. Situations in which this may occur include:

- An individual temporarily had impaired decision-making capacity when initially enrolled in a study, or was enrolled in a study conducted in an emergency setting.
- A subject participates in a longitudinal study. If any study is particularly long, re-consent from the subject may be necessary to maintain a subject's understanding of the relevant research activities. PIs should present a plan for maintaining informed consent when submitting protocols where subjects will be followed over extensive periods of time.
- A minor is enrolled in a study and reaches the age of majority while still participating in the research, including access to medical records only. Failure to obtain the consent of the participant at age 18 years requires discontinuation/removal from further study participation.

Elements of Informed Consent[56, 57]

Please refer to CHA policy A-COM-0004 (Informed Consent for Research and Authorization for the Use and Disclosure of Protected Health Information) for complete details of the required elements of informed consent.

The IRB will ensure that the required elements of consent, per 45 CFR 46 and 21 CFR 50.25, are present in the approved ICF and that it provides adequate information to the subject or his/her LAR regarding the following:

- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;
- A statement that the study involves research, an explanation of the purpose of the research, the expected duration of participation, a description of the procedures, and identification of any experimental procedures;
- A description of any reasonably foreseeable risks or discomforts;
- A description of any benefits to the subject or to others that might be reasonably expected from the research;
- Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject, including no treatment or not participating in the research.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that records may be examined by the sponsor, the IRB, the FDA, or other regulatory agencies;
- For research involving greater than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to questions about the research and research subjects' rights, and whom to contact if the subject sustains a research-related injury;
- One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

  (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another

[56] OHRP Informed Consent Checklist – Basic and Additional Elements

[57] FDA Guide to Informed Consent – Information Sheet Guidance for IRBs and Clinical Investigators

investigator for future research studies without additional informed consent from the subject or the LAR, if this might be a possibility; or

(ii) (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

One or more of the following elements of information, when appropriate, shall also be provided to each subject or the LAR following:

- A statement that the particular procedure or treatment may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant or is a man capable of fathering a child) that are currently unforeseeable;
- Anticipated circumstances under which the subject's participation may be terminated by the PI without regard to the subject's consent;
- Any costs to the subject that may result from participation in the study;
- The consequences of a subject's decision to withdraw from the research and procedures for safe and orderly termination of participation;
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue to participate, will be provided to the subject;
- The approximate number of subjects involved in the study, including at CHA.
- Clarification whether the investigational drug, device, or biologic involved in a study will be available to a subject after the subject has completed the study, or if the study is terminated.
- An explanation of the payment plan or a statement that subjects will not be paid for participation.
- An estimate of any hazard associated with exposure to ionizing radiation as a result of participation in the study. The assessment should be in lay language and contextualize the exposure (*e.g.*, a multiple of the background radiation to which people are exposed in one year).
- A statement as to whether human genetic/research testing is associated with the protocol, and if so an explanation of potential relevant risks to the subject and relatives.
- A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

A study participant or his/her LAR can revoke the subject's consent to participate in the research and/or authorization to use and disclose the subject's PHI. This can be done by the subject or his/her LAR telling a member of the study team that the subject no longer wishes to participate in the study.

Communicating New Information to Study Subjects

In accordance with Federal regulation it may be necessary for subjects to be notified of new information learned during the course of a study. The IRB will consider the need to obtain and document this notification on a protocol-by-protocol basis.

The PI is to submit to the IRB office for review and approval the required documentation to amend the study, including a tracked revised protocol reflecting the information to be communicated, the timeframe in which that is to occur, and the method and procedures by which that will occur. An ICF or similar document that conveys the information and documents the subject's or his/her LAR's signature as attestation of receipt of the information similarly requires IRB review and approval prior to use.

Responsibilities for Reviewing ICF(s)

IRB office staff may perform an initial screening of an ICF(s) in the context of the proposed research. To the extent possible, IRB office staff will notate the ICF with suggested language, inconsistencies between the ICF and protocol, *etc*. This notated ICF should then be supplied to the IRB reviewer, and if the research is reviewed by the convened IRB, the IRB members.

It is the responsibility of the reviewer(s) to review the ICF(s) as described elsewhere in this manual.

Documentation and Waiver of Informed Consent

Please refer to CHA policy A-COM-0004 (Informed Consent for Research and Authorization for the Use and Disclosure of Protected Health Information) for details of this policy, including criteria for waiver or alterations of informed consent.

In accordance with 45 CFR 46 and 21 CFR 50.27, except as provided below, informed consent must be documented by the use of a written ICF approved by the IRB and signed (including in an electronic format) by the subject or the subject's LAR. A written copy shall be given to the person signing the informed consent form.

The original signed ICF(s) should be kept by the PI in a secure location for a minimum of 7 years, or more if required by the FDA or sponsor, following completion of the research. For an active, on-going study, the PI should be able to access executed ICF(s) in a reasonable amount of time, if requested. A copy of the executed ICF(s) is to be given to the person signing the ICF(s). When the study involves treatment intervention the CHA IRB recommends that the PI also file a copy of the subject's executed ICF in his/her medical record.

An ICF may be either of the following:

- A written ICF in a language understandable to the subject that embodies the elements of informed consent required by Federal regulation and as outlined in this manual. The investigator is to give either the subject or the subject's LAR adequate opportunity to read the informed consent form before it is signed or the ICF may be read to the subject or the subject's LAR.

OR

- A short form written ICF stating that the elements of informed consent required by 46.116 have been presented orally to the subject or the subject's LAR and that the key information required by 45 CFR 46 was presented first to the subject, before other information, if any, was provided. The IRB shall approve a written summary of what is to be said to the subject or the LAR. When this method is used, there is to be a witness to the oral presentation. Also, the IRB is to approve a written summary of what is to be said to the subject or the LAR. Only the short form itself is to be signed by the subject or the LAR. However, a witness is to sign both the short form and a copy of the summary. The person actually obtaining consent is to sign a copy of the summary. The PI should keep the original signed documents and copies of the documents are to be given to the subject or the subject's LAR, in addition to a copy of the short form. Additional information and detail regarding short form ICF use is below.

In accord with 45 CFR 46, the IRB may approve a study in which PI will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's LAR, if either of the following conditions are met:

(1) The PI will obtain information through oral or written communication with the prospective subject or LAR, or

(2) The PI will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

While FDA regulations do not permit modifications or waivers of informed consent requirements, except for emergency use of test articles, which are exempt from prior IRB review (refer to other sections of this manual), an IRB may waive the requirement for an investigator to obtain a signed ICF for some or all subjects if it finds and documents any of the following are true:

- The only record linking the subject and the research would be the ICF and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject or LAR will be asked whether the subject wants documentation linking the subject with the research, and the subjects' wishes will govern.

OR

- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

- If the subjects or LARs are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects or LARs with a written statement regarding the research.

In accordance with CHA policy A-COM-0004 (Informed Consent for Research and Authorization for the Use and Disclosure of Protected Health Information), waiver or alterations of informed consent will be granted on a case-by-case basis at the discretion of the IRB Chair or designee, or convened IRB. In such cases, the IRB may require the PI to provide subjects with a written statement/summary explaining the research. This waiver will be documented for protocols approved by expedited procedures, and documented in the minutes for protocols approved by the convened IRB.

Informed Consent for Subjects who do not Understand English [58,59] and Short Form Use

When enrolling a non-English speaking person into a study, the informed consent information needs to be presented in a language understandable to the subject and documented (DHHS: 45 CFR 46, FDA: 21 CFR 50.25 and 21 CFR 50.27).

In the event of unplanned enrollment of a subject who does not understand written English, the institutions caution investigators to carefully consider the ethical/legal implications of enrolling subjects who do not understand English. If the subject does not understand the information presented, the subject must not be enrolled in the study.

The 2 main options for written consent are:

1. The entire written IRB-approved English ICF may be translated into the language understandable to the subject.

OR

2. Oral presentation of informed consent information with a "short form" may be used.

If a study will enroll only a specific non-English speaking population, translation of the entire IRB-approved English ICF is required. Also, if it is expected that more than 5 persons of a specific non-English speaking population will be enrolled, an ICF in the specific foreign language should be developed for use.

2. Use of a Translated Short Form

To ensure that non-English speaking persons are not excluded from participating in research a “short form” may be used. At CHA every study is eligible to use a short form ICF unless the IRB specifically documents that a short form may not be used in a study. Under certain circumstances, the IRB may not allow the use of a short form ICF, for example based on the level of risk associated with the study (*e.g.*, a gene transfer study).

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[58] OPRR guidance, Obtaining and Documenting Informed Consent of Subjects who do not Speak English, 09 November 1995

[59] FDA Guide to Informed Consent – Information Sheet Guidance for IRBs and Clinical Investigators

Use of a short form is allowed unless specifically stated otherwise in the IRB minutes and *Notice of IRB Approval* letter.

A signed short form essentially documents the oral presentation of the entire written IRB-approved English ICF in a language understandable to the subject. For industry sponsored research, PIs are advised to confer with the sponsor prior to the enrollment of a non-English speaking subject and obtain the sponsor's support for such enrollment.

The IRB has approved an English short form for use at CHA and has had the document translated to several languages and posted on the IRB website. Up to 5 short forms in the same language may be used in a study in a twelve (12) month period.

As with consent of English speaking persons, the IRB will count every subject who has signed a short form as enrolled, whether or not that subject completes the study. That is to say, that each signed short form "counts" toward the 5 that may be used in a study in a 12-month period.

To help a non-English speaking subject get translation help to telephone the PI, if needed, the IRB has also created and translated a short page called "Directions for help to speak with a research study PI." This page should be given to the enrolled subject in a language s/he understands.

When using a short form with a non-English speaking person, **ALL** of the following must be completed:

- The subject must be given a copy of the short form in the language understandable to him/her to read.
- A translator/interpreter who is fluent in the subject's language and English must orally present the entire IRB-approved English ICF to the subject in a language understandable to the subject.
- Note: A family member of a subject can act as a translator/interpreter. If a member of the research team is fluent in the language understandable to the subject and English s/he can act as the translator/interpreter and the Person Obtaining Consent; however, s/he may not also act as the witness.
- The entire consent process must be witnessed by an individual who is fluent in both English and the language understandable to the subject.
- Note: The witness may be staff, the translator/interpreter, a family member, or another person. A member of the study staff acting as translator/interpreter and Person Obtaining Consent is not to also serve as the witness. Before starting the consent process, the PI is to verify whether the translator/interpreter will also be able to serve as a witness. If not, another person will be needed to serve as the witness.
- The IRB-approved English ICF must be signed by the investigator authorized to obtain consent and the witness to the consent process.
- The short form in the language understandable to the subject must be signed by the subject, the investigator authorized to obtain consent, and the witness to the consent process (see above).
- The subject must be given signed copies of both the IRB-approved English ICF (the summary) and the short form in the language understandable to the subject; **AND**
- The original signed English ICF and the original signed short form should be placed in the subject's study record and a copy of both placed in his/her medical record, if appropriate.

During the consent process the translator/interpreter should briefly explain the consent process to the prospective subject. The prospective subject's questions or concerns should be relayed by the translator/interpreter to the person obtaining consent, and the answers translated back to the prospective subject. Adequate time should be afforded the participant to make an informed decision regarding participation in the study.

Investigators are also advised to consult Federal guidance on this topic if in doubt.[60] [61]

3. Enrollment of Persons who Understand English but cannot Talk or Write or are Illiterate[62,63]

Persons who speak and understand English, but cannot not read and/or write may be enrolled in a study by "making a mark" on the ICF. This includes persons who are illiterate as well as persons who are physically unable to talk or write, but are competent and able to indicate approval or disapproval by other means.

If a person is physically unable to talk or write, but is competent, able to understand the concepts of the study, and able to evaluate the risk and benefit associated with being in a study when it is explained, and is able to indicate approval or disapproval to study participation, the person may be enrolled into the study. In such a case, an impartial third party should witness the entire consent process and sign the ICF. A video tape recording of the process is recommended, per FDA guidance. If a PI chooses to video record the consent process, s/he must obtain IRB approval for the taping and the subject must consent to the taping. The PI should keep the tape on file with the other study documents.

Alternatively, if an individual is physically able to talk or write but is illiterate, Federal regulations (45 CFR 46, 21 CFR 50.27) permit oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. The oral presentation and the short form written document should be in a language understandable to the subject. The IRB-approved English language ICF may serve as the summary. An impartial third party is to witness the entire consent process. This process is detailed elsewhere in this manual.

The name of the subject should be printed on the short form document and after the oral presentation the subject is to "mark" it, *e.g.*, with an "X." The witness is to sign the short form document and the summary. The person who obtains consent is to sign a copy of the summary. When a translator assists the person obtaining consent, the translator may serve as the witness. The impartial third party witness is to sign the ICF.

The subject must be given copies of the signed short form document and the summary.

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[60] FDA: Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors

[61] OPRR: Obtaining and Documenting Informed Consent of Subjects Who do not Speak English, 09 November 1995

[62] OPRR guidance, Obtaining and Documenting Informed Consent of Subjects who do not Speak English, 09 November 2005

[63] FDA Guide to Informed Consent – Information Sheet Guidance for IRBs and Clinical Investigators

The PI should record a detailed summary of the enrollment of such subjects in the study files and report the enrollment to the IRB and sponsor, if applicable.

The IRB is to receive a copy of the short form document. In addition, the IRB must approve a written summary of what is to be presented orally and the protocol must include a discussion on how the oral consent process will be conducted.

The IRB expects a PI and study staff to be extra vigilant when an illiterate person is enrolled in a study and must ensure that the subject clearly understands study instructions during the course of the study.

Any subsequent revisions to the ICF must be explained and witnessed in a similar manner.

4. Translation of Study Documents

21 CFR 50.20, 45 CFR 46.116, and 46. 117 require that study-related information that is given to a subject or a subject's LAR be in language understandable to the subject or the representative.

When a PI plans to regularly enroll non-English speaking subjects, documents should be prepared in the applicable native language. These documents must be approved by the IRB. Federal guidance[64] [65] provides no specific details about how the IRB should verify that the document is intelligible to the subject and/or is culturally sensitive.

This policy applies when part or all of a prospective study population does not speak or read English, or minimally speaks or reads it.

The IRB will review and approve the English version of the document(s) (*e.g.*, ICF, advertisements, subject education material, contact letters, questionnaires). The review may be either expedited or by the convened IRB depending on the nature of the material and in accordance with Federal guidance and regulations. All documents must satisfy IRB standards for language reading level and required elements of consent, *etc.* The IRB-approved and validated English document(s) may then be translated into a subject's primary language. The translated material should then be back translated into English to confirm that the meaning has not been changed. Request for back translation will be at the discretion of the Reviewer.

All translations are to be performed by the CHA department of translation services (*i.e.,* Multicultural Affairs and Patient Services). If an investigator receives a document that has already been translated, the translation is to be reviewed and verified by a qualified member of the CHA Multicultural Affairs and Patient Services. The review and verification should be documented in writing and signed by the member of the CHA Multicultural Affairs and Patient Services.

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[64] OPRR guidance, Obtaining and Documenting Informed Consent of Subjects who do not Speak English, 09 November 2005

[65] FDA Guide to Informed Consent – Information Sheet Guidance for IRBs and Clinical Investigators

A PI may not use the translated documents (ICFs, advertisements, patient education material, contact letters, *etc.*) until they are approved and validated by the IRB.

In addition to standard ICF elements, translated documents should be at a reading level appropriate to the subject. For studies being conducted with subjects with a lower literacy level than 7th grade, a lower reading level may be required. Language choice should be culturally sensitive to the population expected to read the document.

5. Vulnerable Populations

As required by Federal regulation, when some or all subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, economically or educationally disadvantaged persons, students, or employees, the IRB will ensure that appropriate additional safeguards will be included in the protocol to protect the rights and welfare of these subjects.

Women and Minorities in Research

The IRB will not unnecessarily exclude women or other subject populations from research.

Women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes exclusion. Exclusion under other circumstances may be made based on a compelling rationale and justification. The IRB will not accept cost as an acceptable reason for exclusion except when the study would duplicate data from other sources.

Woman of child bearing potential must not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subject of all ages.

The inclusion of women and members of minority groups and their subpopulations should be addressed when developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population, including gender and racial/ethnic group, and provide a rationale for selection of the subjects.[66] [67] [68]

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[66] Inclusion of Women and Minorities As Participants In Research Involving Human Subjects - Policy Implementation Page, NIH Guidance, Inclusion of Women and Minorities as Subjects in Clinical Research

[67] NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Policy Implementation

[68] NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October 2001

Women may be enrolled in any type of research, including Phase I and early Phase II studies.[69] According to the FDA, early drug and biologic studies can be safely conducted in women even before completion of all animal reproduction studies through protocol designs that include monitoring for pregnancy, as well as measures to prevent pregnancy during exposure to investigational agents. When women will be enrolled in a study, the IRB will give special consideration to pregnancy testing. Women should be counseled about the reliable use of contraception or abstinence from intercourse while participating in a study, as appropriate. The type and duration of contraception to be used should be stated in the protocol, and should be determined in consultation with the woman, the PI, and/or her health care provider. These provisions should also be clearly outlined in lay language in the ICF.

For many approved substances, current information regarding drug effects in pregnancy and lactation is available through established databases such as Reprotox. When such information is available, it should be included in the ICF, and updated as needed. When preclinical teratology and reproductive toxicology data are not available, the PI should ensure that male and female subjects are informed about potential effects of a test article on conception and fetal development. All study subjects should be provided with new pertinent information arising from preclinical studies as it becomes available and the ICF should be updated when needed. Study subjects should also be informed about any new clinical data that emerge regarding general safety and effectiveness, including relevant gender effects.

Many investigators seek to obtain information regarding pregnancies in female partners of male study subjects who conceived while the study subject was taking the study agent. If this may place the partner or future child at risk, consideration should be given to providing written information to the partner at the time the subject is enrolled. If so, this information sheet must be reviewed and approved by the IRB. Similarly, if the partner does conceive, and the PI seeks information about the pregnancy, an IRB approved information sheet should be given by the subject to the partner, offering the partner the opportunity to consent to release information. Partners of study subjects are not research subjects and cannot be required to release information and neither the PI nor the sponsor may directly contact the partner.

Pregnant Women, Fetuses, and Neonates

The IRB will review research involving pregnant women, fetuses, or neonates in accordance with Federal regulations (45 CFR 46, subpart B) and state statutes.

The Massachusetts Fetal Research Statute (M.G.L ch.112, section12J)[70] limits research on neonates (minors under 28 days of life). M.G.L. ch.112, section12J states, in part:

> "This section shall not prohibit or regulate diagnostic or remedial procedures the purpose of which is to determine the life or health of the fetus or neonate involved, or to preserve the life or health of the fetus or neonate involved or the mother involved, or to improve the chances of a viable birth for a fetus with a congenital or other fetal conditions that would

[69] Guidance for Institutional Review Boards and Clinical Investigators 1998 Update, Drugs and Biologics, Evaluation of Gender Differences in Clinical Investigations, FDA

[70] The General Laws of Massachusetts, Title XVI. Public Health: Chapter 112: Section 12J. Experimentation on human fetuses prohibited; medical procedures authorized; consent; approval; civil and criminal liability and proceedings; severability

otherwise substantially impair or jeopardize the fetus's health or viability, or research approved by an Institutional Review Board applying Federal regulations for the protection of fetuses and neonates, that are conducted for the purpose of developing, comparing or improving diagnostic or therapeutic fetal or neonatal interventions to improve the viability or quality of life of fetuses, neonates and children."

This will be assessed at the time of study review and appropriate findings will be made and documented. To aid in the IRB's determination, at the time of study submission the PI is encouraged to include an explanation in the protocol of how the research is in conformity with the statute. In practice, findings related to M.G.L. ch.112, section12J are made prior to Federal findings; unless the state statute provisions can be satisfied, the research cannot be conducted.

Findings will be made and protocol-specific justifications based on discussion at a convened IRB meeting will be documented in the IRB meeting minutes.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

a. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

b. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means;

c. Any risk is the least possible for achieving the objectives of the research;

d. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with informed consent requirements described elsewhere in this manual;

e. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of 45 CFR 46 (the "Common Rule"), except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;

f. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

g. For children, as defined elsewhere in this manual, who are pregnant, assent and permission are obtained per Federal regulation;

h. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

i. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

j. Individuals engaged in the research will have no part in determining the viability of the neonate.

When neonates of uncertain viability and nonviable neonates may be involved in research, all of the following conditions must be met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate; and

3. Individuals engaged in the research will have no part in determining the viability of the neonate.

Until it has been determined whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

(1) The IRB determines that:

(i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's LAR is obtained as discussed elsewhere in this manual, except that the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

After delivery, a nonviable neonate may not be involved in research unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;

2. The research will not terminate the heartbeat or respiration of the neonate;

3. There will be no added risk to the neonate resulting from the research;

4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

5. The legally effective informed consent of both parents of the neonate is obtained as discussed elsewhere in this manual, except that the waiver and alteration provisions of 45 CFR 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate is sufficient to meet the requirements, except that the consent of the father does not need to be obtained if the pregnancy resulted from rape

or incest. The consent of a LAR of either or both of the parents of a nonviable neonate will not be sufficient to meet the requirements.

A neonate that has been determined to be viable after delivery may be included in research only to the extent permitted by and in accordance with 45 CFR 46 subparts A and D.

In accordance with 45 CFR 46.206, research involving a placenta, a dead fetus or fetal material, macerated fetal material, or cells, tissue, or organs excised from a dead fetus, after delivery, will be conducted only in accordance with any applicable Federal, state, or local laws and regulations regarding such activities.

If information associated with material described above is recorded for research purposes such that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects. As a result, a separate research application must be submitted to the IRB for review and approval.

Minors

Children are defined as "persons who have not attained the legal age for consent to treatments or procedures involved in the research." Under Massachusetts law, children are individuals less than 18 years of age, with the exception of emancipated minors and neonates 28 days and younger. Studies involving children are strictly regulated. When reviewing a protocol including children, the IRB must classify the research into 1 of 4 categories per 45 CFR 46 subpart D. IRB meeting minutes must document the category under which the protocol is approved. The categories of research involving children are based on potential risk and benefit to individual subjects and are as follows:

45 CFR 46.404, 21 CFR 50.51 — Research not involving greater than minimal risk.

45 CFR 46.405, 21 CFR 50.52 — Research involving greater than minimal risk, but presenting the prospect of direct benefit to individual participants can be approved only if all of the following are true:

- The risk is justified by the anticipated benefit to the subjects.
- The relation of the anticipated benefits to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

45 CFR 46.406, 21 CFR 50.53 — Research involving greater than minimal risk and no prospect of direct benefit to individual participants can be approved only if all of the following are true:

- The risk represents a minor increase over minimal risk.
- The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.
- The intervention or procedure is likely to yield knowledge about the subjects' disorder or condition that is of vital importance for the understanding of the participant's condition.

45 CFR 46.407, 21 CFR 50.54 — Research that does not fall into 1 of the 3 categories above, but which the IRB finds presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or

welfare of children cannot be approved by the IRB acting alone, but requires the approval of the Secretary of the DHHS.

In accordance with Federal regulations (45 CFR 46.408, 21 CFR 50.55) the IRB must ensure that a study includes procedures for obtaining the assent of the child, as well as the permission of the parent(s) or legal guardian(s). Assent refers to a child's agreement as distinct from consent, which is legally valid.

Per institutional policy, the assent of a minor is to be solicited if the minor is aged 7 years or older and is of appropriate maturity and psychological state. A minor has the right to refuse to participate. However, if the IRB determines that the capability of some or all of the minors is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available *only* in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord Federal regulations.

Taking into account the age, maturity, and psychological state of the minor involved, s/he is to be provided with an explanation of what participation will involve and the minor is to be given the opportunity to read the ICF(s). Sample minor assent documents have been developed by the IRB and are tailored based on age appropriate reading level. The templates are available on the IRB website on staffnet. While regulation does not require a minor to provide signed assent, signed assent from the minor should be documented on the ICF or on a separate assent form, if appropriate based on age, maturity, etc. Regardless, it is the responsibility of the PI to propose in the protocol the assent process, including how assent will be documented by the study team.

If a minor is enrolled in a study s/he must provide consent at age 18 years to continue study participation.

In certain instances, a minor legally may be considered an "emancipated minor" (*e.g.*, a pregnant minor) and may consent on his/her own behalf without parental involvement. These instances are evaluated on a case-by-case basis, and frequently require obtaining opinion from legal counsel. Considerations given to approval of an emancipated minor consenting to participate in research includes the nature of the research, potential benefit of the research, and potential harms in seeking a parent or guardian's approval, as well as applicable state laws.

After review of the information submitted by the PI, it is the responsibility of the IRB to determine whether the permission of 1 parent/guardian or 2 parents/guardians is required:

In accordance with 45 CFR 46.404, 21 CFR 50.51 and 45 CFR 46.405, 21 CFR 50.52 the permission of 1 parent/guardian and the minor's assent is sufficient.

In accordance with 45 CFR 46.406, 21 CFR 50.53 and 45 CFR 46.407, 21 CFR 50.54, the permission of 2 parents/guardians and the minor's assent is required.

Where permission is to be obtained from both parents/guardians, both parents/guardians must give their permission unless 1 parent is deceased, unknown, incompetent, or not reasonably available, or when only 1 parents has legal responsibility for the care and custody of the child.

At its discretion, the IRB may require the signature of 2 parents/guardians in particular situations even though 1 signature is sufficient under the regulations.

Employees and Students

Per Federal regulations, informed consent must be sought in circumstances where the possibility of coercion or undue influence of a prospective subject is minimized.[71] CHA considers employees and students to be potentially vulnerable subject populations.

As a result, the IRB must ensure that a PI who plans to actively recruit students and/or staff clearly defines the rationale for such participation in the protocol. In addition, details about the recruitment strategies are to be stated in the protocol.

When employees and/or students will be enrolled, a letter from the appropriate institutional official (*e.g.*, Dean, Department Chair, Vice-President) attesting to the fact that the project is acceptable and that coercion has been minimized may be a condition of approval. If residents or fellows will be enrolled in a study, the Program Director may be asked to provide the IRB with a similar letter of support. The letter must be from an institutional official not involved in the research (*e.g.*, if the program director is conducting research that will enroll residents, the letter must come from the Department Chair or institutional official for graduate medical education).

Of particular consideration for the IRB when employees or students are specifically targeted for study enrollment is the issue of study data confidentiality. Depending on the nature of the research and the data collected, a breach of confidentiality could affect a person's employment, career path, educational plans, or social relationships within the CHA community. The IRB will also give special consideration to a PI's proposed plan for data security.

Prisoners

Per 45 CFR 46.107, 45 CFR 46.301-306 (subpart C), 21 CFR 56.107, and 21 CFR 56.111, when the IRB reviews research involving prisoner subjects at least 1 of the members who participates in the review of the research will be a prisoner or prisoner representative with appropriate background and experience to serve in that capacity. In situations where a particular research project is reviewed by more than 1 IRB, only 1 IRB need satisfy this requirement.

"Prisoner" is defined to include any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Investigators who plan to conduct research that will enroll prisoners should contact the IRB early in the planning process so that appropriate arrangements may be made for review.

When prisoners will be enrolled the IRB must find and document in the minutes that the research is within a permissible category of 45 CFR Part 46.306(a)(2), which includes:

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[71] 21 CFR 50.20, 45 CFR 46.116, 45 CFR 46.111

- Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.

- Study of prisons as institutional structures, or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.

- Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is more prevalent in prisons; and research on social and psychological problems such as alcoholism, drug addiction or sexual assaults). The study may proceed, however, only after the DHHS has consulted with appropriate experts including experts in penology, medicine and ethics, and published notice in the Federal Register of its intent to approve such research.[72]

- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. If the research involves a control group whose members may not benefit from the research, the study may proceed only after DHHS has consulted with the appropriate experts discussed above.[40]

In reviewing such research proposals, the IRB must make and document the following determinations:

- Any possible advantages a prisoner may accrue through his/her participation in the research when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his/her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.

- The potential risks associated with the research are commensurate with risks that would be accepted by non-prisoner volunteers.

- Procedures for the selection of subjects within the prison are fair to all prisoners and free from arbitrary intervention by prison authorities or prisoners. Unless the PI provides justification in writing to the IRB for following alternative procedures, control subjects must be selected randomly from the group of available prisoners who meet the eligibility criteria for the research project.

- The information is presented in language that is understandable to the subject population.

- Adequate assurance exists that in making decisions regarding parole, parole boards will not take into account a prisoner's participation in the research and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.

Where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

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[72] For non-DHHS-supported research, OHRP recommends the research proceed only after the IRB has consulted with appropriate experts, as determined by the IRB.

Impaired Decision-Making Capacity

When reviewing research that will enroll subjects with temporary or permanent impaired decision-making capacity, the IRB must consider additional necessary protections.

Massachusetts law regulates the involvement of clients of the Department of Mental Health in research protocols.

In addition to the mentally impaired, some persons may temporarily or permanently have a diminished capacity to understand information presented or to make a reasoned decision to participate in research due to a stroke, head injury, or other acute condition.

In general, only persons who are competent, *i.e.*, those with the capacity to provide informed consent to participate in research, may be enrolled in a protocol, unless the PI explicitly requests in writing, and the IRB explicitly approves, enrollment of persons with impaired decision-making capacity.

The IRB will consider the following when a study seeks to enroll temporarily or permanently decisionally impaired persons:

- The number of subjects to be enrolled and the biological or social attributes that will define their eligibility for participation in the protocol. An explanation of the rationale for including such subjects considered mentally impaired should be provided by the PI. Suitable justification may include the following:
    - The purpose of the research is to develop knowledge that one can reasonably expect could benefit the class of persons that the subject represents,
    - The research is designed to study the safety and efficacy of a therapeutic modality that is likely to bring direct benefit to the individual subject,
    - Preliminary studies already have been performed on less vulnerable subjects,
    - The protocol is designed to study conditions that do not affect less vulnerable populations.
- The research may not present greater than minimal risk to subjects, unless the research offers the prospect of direct benefit to each individual subject. However, the IRB will consider enrollment of a person with impaired decision-making capacity in a minimal risk study (*e.g.*, observational study, registry) provided the LAR of the person with impaired decision-making capacity provides permission and, if able, the person with impaired decision-making capacity provides assent.
- Prior to enrollment of persons with diminished capacity, the PI must determine whether the subject is competent to provide informed consent. Competence may be defined as an ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to express a choice. In some cases, the IRB may request that a person(s) independent from the research study evaluate the subject to determine competence. The IRB may also require the presence of a consent monitor to assure that the subject(s) understands the research and that s/he is free to decline to participate, particularly in situations in which purely research interventions may be misunderstood by subjects as treatment.

If the study is greater than minimal risk the IRB meeting minutes will record whether the IRB has approved the enrollment of subjects with impaired decision-making capacity. The minutes may include additional findings regarding under what circumstances they may be enrolled, any need to re-consent subjects as their

decision making capacity improves, qualifications of the person determining the degree of competence, need for assent, *etc*. If the study is minimal risk and seeks to enroll persons with impaired decision-making capacity, the Reviewer will specifically document approval to enroll this vulnerable population.

6. International Research

Any international research that a CHA faculty member, employee, *etc.*, is involved with must be reviewed and approved by the CHA IRB, in addition to an IRB/ethics committee in the host country, before any research-related activities may begin. Required documents for submission are discussed elsewhere in this manual.

If a CHA faculty member, employee, *etc.*, becomes involved after the international research has been initiated, approval from the CHA IRB is required at the time of the investigator's involvement. The CHA PI is to provide a letter specifying when s/he became involved with the international research and delineate the components of the research that s/he will be involved in; this letter will be part of the IRB study file.

Any international human subject research in which CHA investigators are involved, and which would be subject to Federal regulations if it were conducted entirely in the United States, is to comply with the Federal regulations for the protection of human subjects in all material respects, unless otherwise waived by the CHA IRB.

Procedures normally followed in the country where the research will take place may differ from those in US Federal regulations. Therefore, in accordance with US regulations, research may be approved if "the procedures prescribed by the [foreign] institution afford protections that are at least equivalent to those" outlined in Federal regulation. In such a case, the foreign country's procedures may be substituted for the procedures required by the Federal regulations.

Any international research that is funded by the FDA must comply with both DHHS and FDA regulations.

To ensure the IRB has the necessary information to review an international research project application should detail the PI and research team's experience and qualifications to conduct research in the foreign country, clearly detail what procedures will be conducted at specific locations, and details about any pertinent local laws in the foreign country that differ with US laws.

Approval from an IRB/ethics committee in the host country will be a requirement for approval by the CHA IRB.

Per DHHS communication, the requirements of DHHS regulations must be satisfied for all DHHS-conducted or –supported research covered by a FWA regardless of whether the research is conducted domestically or internationally.[73]

As Federal guidance addressing international research is periodically released, Investigators involved in international research are advised to consult Federal sources, including the *International Compilation of Human Subject Research Protections* guidance document.[74]

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[73] DHHS Protection of Human Subjects: Interpretation of Assurance Requirements, Federal Register, Vol. 71, No. 130, 38645, 07 July 2006

7. Ionizing Radiation

X-rays, computed tomography (CT) scan, bone densitometry, mammography, all nuclear medicine procedures, and all radiation therapy procedures emit ionizing radiation. Any research that involves subject exposure to ionizing radiation for research purposes will be forwarded to the convened IRB for review. If the ionizing radiation exposure is for clinical purposes, not research, the study may be reviewed by expedited review provided it meets the requirements for expedited review.

When subjects will be exposed to ionizing radiation for research-related purposes only, the institutional RSO's review and acceptance of the ionizing radiation exposure(s) will be required. The RSO will review and, if indicated, suggest appropriate language describing the radiation exposure for the ICF. The PI is to include any such language in the ICF.

Neither Magnetic Resonance Imaging (MRI) nor ultrasound imaging involves ionizing radiation.

8. Massachusetts Controlled Substances Researcher Registration

Pursuant to Massachusetts General Law (MGL Chapter 94C, §7, MGL Chapter 94C, §8), a Massachusetts Department of Public Health Controlled Substances Researcher Registration will be obtained when human research involves investigational and/or approved drugs for new indications. If the registration is held by a Department Chair, it will extend to all faculty members within a registered department.

A Chair/Chief, or other qualified applicant, is responsible for completing the necessary applications and the accuracy of the information in the form(s). The original Massachusetts Controlled Substances Researcher Registration is to be retained by the applicant and a copy should be forwarded to the IRB office for file.

9. IRB Administrative Fee

Administrative fees may be charged to any industry-sponsored human research study to offset the costs of maintaining the human research protection program. A fee will not be applied to Federal or foundation funded studies. Institutional leadership will determine the fee(s), which is processed by the Office of Sponsored Research.

10. Certificate of Confidentiality

A National Institutes of Health Certificate of Confidentiality (CoC) protects identifiable research information from forced disclosure in any civil, criminal, administrative, legislative, or other proceeding, whether Federal, state, or local.[75] As of October 1, 2017, all NIH-funded research that collects or uses identifiable, sensitive information will automatically be issued a CoC. Note: This policy was retroactive to all NIH-funded research

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[74] International Compilation of Human Subject Research Protections

[75] National Institutes of Health Office of Extramural Research, Certificate of Confidentiality Kiosk

that was commenced or ongoing on or after December 13, 2016 and otherwise falls under the policy; such research was deemed to have been issued a CoC.

On a case-by-case basis the IRB will assess whether a CoC is needed, regardless of funding source. A PI may be required by the IRB to obtain a CoC as a condition of approval as outlined in Federal guidance. Such a requirement will be documented by the IRB and will be communicated to the PI. If a CoC is obtained, the NIH-required consent language is to be included in the ICF.

11. Subject Complaints

Any communication received in the IRB office from a subject will be called to the attention of the HRPP Manager or his/her designee. S/he will review the nature of the communication and will contact the subject, if required. If needed, the PI will be contacted to obtain additional information. A summary of the incident and communications will be recorded in the associated IRB study file. At the discretion of the IRB Chair a subject complaint may be reported to the convened IRB and/or IO.

12. Transferring Research to another PI

If a PI leaves CHA and/or is no longer a member of the CHA faculty or staff, then his/her IRB-approved research must be either transferred to a qualified PI at CHA or must be terminated.

When a PI chooses to transfer his/her role as PI to another person, the IRB is to be notified with an amendment submission. The new PI must be eligible to serve as a CHA PI. The new PI must submit or have submitted the appropriate COI forms, must have documentation that she has completed the required CHA research education, and must have the necessary licenses and privileges required to serve as PI of the research protocol, as applicable. Appropriate changes to the ICF, recruitment materials, *etc.* must be submitted with the amendment. The new PI is notified of the IRB approval of the change in PI.

13. Investigating and Reporting Research Non-Compliance

In this policy, non-compliance means failure of a PI or members of a study's research team to comply with Federal or state regulations or institutional policies or guidelines related to human subject protection or with the requirements or determinations of the IRB.

Incidents of possible non-compliance may be identified through internal audit, during the course of routine IRB business, by PI self-report, by report from another investigator/research team member, from a subject or subject family complaint, or by other means.

A PI and research team is expected to cooperate with any non-compliance investigation and to provide any information requested of him/her as part of an investigation. Continued lack of cooperation or continued failure to provide requested information may be regarded as serious non-compliance with the requirements and determinations of the IRB.

CHA has established 3 levels of research non-compliance, which are outlined below.

Administrative non-compliance: Level 1 (not affecting safety)

Level 1 non-compliance is administrative-related non-compliance that does not affect subject safety, rights, or welfare; it will not involve any violation that is reportable to a Federal agency.

The following are examples of non-compliance that would not or could not affect the rights, safety, or welfare of subjects (Level 1):

- Use of an outdated ICF that is identical to the current IRB approved ICF, or identical in material respects (*e.g.*, change in the name of a research team member).

- Minor over enrollment of IRB-approved accrual goal in a minimal-risk research study.

Level 1 non-compliance events are incidents that are the result of an honest error or misunderstanding.

Such incidents will be reviewed by the IRB Chair and the HRPP Manager. If the incident appears to meet Level 2 or 3 non-compliance, or that is discovered during the course of the review of the incident, it will be addressed according to those descriptions elsewhere in this manual. Otherwise, in collaboration, the 2 parties will make a preliminary assessment whether Level 1 research non-compliance has occurred. If so, they will agree on a course of action and may consult with the Chief Compliance Officer (CCO) prior to moving forward.

The HRPP Manager will gather necessary information and clarification from the PI/research team and will report the information to the IRB Chair. The PI will typically be asked to provide a corrective and preventive action (CAPA) plan to help ensure that incidents of Level 1 non-compliance are not repeated. The IRB Chair and HRPP Manager may make recommendations for corrective action. The PI will be notified in writing of the final resolution, including if his/her proposed CAPA plan has been accepted and/or if an alternative plan is suggested.

The convened IRB will be notified of the event and CAPA at the next IRB meeting. At the time of IRB notification, IRB members may comment on the CAPA, which may influence the management of future events.

Non-compliance of concern: Level 2 (not affecting safety) and Level 3 (affecting safety)

Non-compliance of concern may or may not affect safety, rights, or welfare of research subjects.

Level 2 is non-compliance of concern <u>not</u> affecting subject safety, rights, or welfare; it may involve a violation that is reportable to a Federal agency. Examples include:

- Significant over enrollment of IRB-approved accrual goal;

- Significant delinquency in reporting SAE(s) that did not require changes to the ICF.

When an instance of non-compliance of concern that *does not affect* subject safety, rights, or welfare is reported or learned about, the situation will initially be brought to the attention of the IRB Chair and the HRPP Manager. In collaboration, they will make a preliminary assessment whether research non-compliance has occurred and meets Level 2. If Level 2 non-compliance is suspected, they will draft a proposed course of action, including an investigation plan, and will consult with the Chief Compliance Officer (CCO)/IO prior to moving forward. The CCO/IO will review the proposed plan and the investigation plan will be finalized. The

CCO/IO will evaluate the need to report the incident to other CHA departments and/or officials. If it is instead determined that the incident is Level 1 or 3 non-compliance, or that is discovered during the course of the investigation, the incident will be addressed according to those descriptions elsewhere in this manual.

For Level 2 non-compliance the HRPP Manager will oversee the investigation plan and will report the results of the investigation to the IRB Chair and the CCO/IO. Typically, a PI will be asked to provide a corrective and preventive action (CAPA) plan to help ensure that the non-compliance is not repeated. The CCO/IO and IRB Chair may recommend or require specific corrective action.

Depending on the nature of the event, the IRB Chair or CCO/IO may suggest that the PI voluntarily cease enrollment of new subjects pending resolution of the investigation. The Chair or CCO/IO may also decide to invoke the Involuntary Suspension/Termination policy described elsewhere in this manual.

At the conclusion of the investigation the CCO/IO will make a determination whether the non-compliance involved a reportable event. If the investigation reveals that subject safety was not affected and did not involve a reportable event, the PI will be notified in writing of the determination and that the incident was not reported to the Federal agency(ies). At the next scheduled IRB meeting the IRB will be notified of the event, CAPA, and that the event was not report to Federal agency(ies). At the time of notification, IRB members may comment on the CAPA, which may influence the management of future events.

If the investigation reveals that subject safety, rights, and welfare was not affected, but the CCO/IO determines that it does involve a reportable event, the PI will be notified in writing of the determination and that the incident will be reported to the Federal agency(ies). The CCO/IO may make an initial telephone report to the Federal agency(ies) or may submit written documentation to Federal agency(ies). In either case, such communication will typically occur within thirty (30) days of the decision to report the event. Such a written report will typically include an overview of the non-compliance event, a description of the investigative actions taken, an explanation of why the non-compliance occurred, details of the CAPA that have been or will be taken, and any sanctions imposed. At the next scheduled IRB meeting members will be notified of the event, CAPA, and that the event was report to Federal agency(ies). At the time of notification, IRB members may comment on the CAPA, which may influence the management of future events.

Level 3 is non-compliance of concern that does affect subject safety and/or affects subject rights or welfare; it involves a violation that is reportable to a Federal agency. Examples include:

- Substantial protocol deviations or violations affecting subject safety;
- Delinquent reporting of SAE or unexpected adverse events that would require changes to the ICF or protocol or would cause the IRB to consider suspending or terminating the study for safety considerations.
- An incident of ongoing negligence or willful violation.

An occurrence of non-compliance of concern that *does affect subject safety, rights, or welfare*, Level 3, will be immediately called to the attention of the IO; it will be reported as required by 45 CFR 46 and 21 CFR 56.108(b).

The CCO/IO, IRB Chair, and HRPP Manager will develop a course of action and an investigation plan. The CCO/IO will report the incident to other CHA departments and/or officials, as needed.

The HRPP Manager will oversee the investigation plan and will report the results to the CCO/IO and IRB Chair. If, during the course of the investigation, it is instead determined by the CCO/IO and IRB Chair that

the incident is Level 1 or 2 non-compliance, the incident will be addressed according to those descriptions elsewhere in this manual.

Otherwise, at the conclusion of the investigation the findings will be reviewed with the CCO/IO and IRB Chair and a final course of action determined. As part of the investigation the CCO/IO, IRB Chair, and HRPP Manager may develop recommendations for corrective action or may ask the PI to provide a CAPA plan to help ensure that incidents of non-compliance are not repeated.

The convened IRB will be informed of the incident, including details of the investigation, in a timely manner. The convened IRB may also be asked to provide input on the corrective action and will be updated on the course of the investigation.

The CCO/IO and IRB Chair will render a determination whether the Involuntary Suspension/Termination policy described elsewhere in this manual should be invoked at any time during the course of a Level 3 non-compliance report investigation.

If Level 3 non-compliance is suspected or concluded the CCO/IO will make an initial telephone report to Federal agency(ies), typically within ten (10) business days of establishing that the incident is Level 3 non-compliance, and will submit follow-up written documentation to Federal agency(ies). Such written reports will include an overview of the non-compliance event, a description of the investigative actions taken, an explanation of why the non-compliance occurred, details of the CAPA that have been or will be taken, and any sanctions imposed.

As noted above, the convened IRB will be updated on the course of the investigation and will be notified of the final resolution of the event, including the CAPA plan and the report to Federal agency(ies). IRB members may comment on the CAPA, which may influence the management of future events.

The PI will be informed in writing of the final decisions and resolution of the event, including that the incident was reported to Federal agency(ies).

14. Involuntary Suspension/Termination of Research and Reporting

The IRB has the authority to suspend or terminate approval of a study (45 CFR 46, 21 CFR 56.113). When possible the convened IRB will render such a determination; however, to protect subject safety the IRB Chair or designee may suspend a study without convening an IRB meeting. IRB members will be notified of a suspension at the next scheduled IRB meeting. The Chair or designee may not terminate a study; only the convened IRB can do so.

Suspension/termination may occur due to:

- Unexpected death or serious harm to a subject.
- Unanticipated problems involving serious harm.
- Risk of serious harm to a subject, such as known or suspected contamination of a study drug.
- Failure of a PI to provide information requested by the IRB within a specified timeframe.
- PI and/or a research team member known or potential non-compliance with human subject regulations or the requirements or determinations of the IRB.

- Other circumstances that in the judgment of the IRB, the IRB Chair or designee necessitate suspension/termination to protect subjects from harm.

A PI will be notified in writing by the IRB Chair or designee of a study suspension/termination. In cases of immediate, significant risk to human subjects the IRB Chair or designee may communicate the suspension/termination orally to a PI while written materials are prepared.

When a study is suspended the letter will state if the suspension applies only to the enrollment of new subjects or requires all study procedures involving enrolled subjects to stop.

In the case of a termination, no new subjects may be enrolled and all study activities involving enrolled subjects must stop. On a case-by-case basis, exceptions may be made by the Chair or designee if subjects are receiving intervention that cannot be safely discontinued.

The IRB Chair or designee will immediately notify the IO and the HRPP Manager of a suspension or termination.

The IO will immediately notify by telephone OHRP, FDA, and other appropriate agencies, as required, of the suspension or termination. After the telephone call the IO will send OHRP, FDA, and other appropriate agencies, as required, written documentation regarding the initial action taken. Subject to further investigation, a final report or follow-up letter will be sent to OHRP, FDA, and other appropriate agencies, as required. The initial letter will specify the IRB action taken, the reason for that action, and any additional information the IO deems necessary. In the case of a funded study, the IO will also notify the funding agency.

On a case-by-case basis the IO, with input from the IRB Chair and the HRPP Manager, will determine whether or not study subjects should be notified of the suspension/termination, as well as the content of the notification to subjects, if indicated. IRB members will be informed of any notice given to study subjects.

Study activities cannot resume in a suspended study until the convened IRB has reviewed the circumstances of the suspension and voted at a convened IRB meeting to permit reactivation of the study. The IRB may vote to reopen the study with or without modification, continue the suspension pending further investigation, or terminate the study. If the PI wishes to resume study activities of a study that has been terminated, the PI is to submit a new study application with any necessary revisions for IRB review.

A lapse in IRB approval is not a suspension or termination.

15. Education Requirements

Research Community

Researchers and the institution share responsibility for ensuring that the PI and all other personnel ("research team members") involved in the conduct of human subject research fulfill education requirements in compliance with all applicable laws, regulations and institutional policies.[76]

The institution defines "research team members" as persons who contribute to the design, conduct, or reporting of a research study, have direct contact with study participants[77], contribute to the research in a substantive way, have contact with a study participant's identifiable data or biological samples (e.g., tissue, blood, urine, plasma, saliva), or uses participants' personal information.

For example, a nurse who ordinarily works on an in-patient unit, but becomes involved in a research protocol by obtaining informed consent from participants or follows-up with study participants admitted to the unit to collect study data would be considered a research team member. However, a laboratory technician who works only with de-identified data and does not have any direct study participant contact would not necessarily be considered a research team member. On the other hand, a biostatistician working with identifiable or coded data would be considered a member of a research team.

Due to the variability in situations, it is impossible to define everyone[78] who could be considered a research team member. Some interpretation by PIs will be needed. CHA expects a PI to make a good faith effort to meet the spirit of the research education training requirement by assuring that all members of a research team receive research-related education and training appropriate to their role in the project.

PIs are directed to OHRP's guidance on engagement in research (Guidance on Engagement of Institutions in Human Subjects Research) for additional information in determining who is a research team member and determining who needs to fulfill the education requirements. [79]

Continuing education is required for PIs and research team members every 3 years. The mandatory research education requirements are appended to this manual. Individuals are to retain a copy of their certificate of

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[76] The information provided here is only intended to assist with the definition of the "research team member;" it is not intended to address issues associated with mentorship or authorship.

[77] Exceptions may exist; there will be individuals whose primary contact with a subject is in the context of clinical care, but who may play a minimal role in the research. An example is a phlebotomist collecting blood for a clinical purpose and collecting an additional sample at the same time for a research project. In this case, provided that someone other than the phlebotomist obtained informed consent, and that the phlebotomist is not playing any further role in the research, s/he would not be considered a research team member; the research education requirement would not apply.

[78] People who may be part of a research team could include administrative assistants, co-investigators, collaborators consultants, contractors, consortium participants, data entry/analysis persons, dieticians, fellows, graduate students, interns, laboratory technicians, nurses, post-docs, recruiters, research coordinators/assistants, residents, students, etc.

[79] OHRP Guidance, Engagement of Institutions in Research, 16 October 2008

completion. PIs are required to retain a copy of education certificates for all research team members: These documents are subject to audit.

The institution encourages investigators and research team members to avail themselves of institutional and local resources for additional education opportunities.

IRB Leadership, Members, Office Staff

CHA provides opportunities to the IRB Chair, members, and office staff for continuing education such as education sessions, seminars, conferences, *etc.* Funds and time to attend education opportunities are dispersed as available by the IO.

The IRB Chair and members are to complete research education requirements annually.

16. Who May be a Principal Investigator

A PI is a person who is capable of fulfilling the responsibilities as described below; his/her qualifications will be considered by the Department Chair/Division Chief and will be confirmed as evidenced by the Chair's/Chief's signature on the IRB application form(s) that are submitted for review.

The IRB considers the qualification of a PI on a protocol-by-protocol basis.

17. PI Responsibilities

DHHS and FDA have created a guidance document on PI responsibilities. PIs are strongly encouraged to read the guidance prior to initiating a research study involving humans.

PIs are responsible to:

- Protect the rights, safety, and welfare of research subjects.
- Abide by Federal and state regulations and ICH guidelines for GCP governing human subject research and informed consent.
- Conduct a research study according to the IRB approved protocol.
- Communicate new information, including safety information, developed during the course of a study that may relate to a subject's willingness to continue participation in a study.
- Ensure all research team members are qualified by education, training, orientation to the study protocol, and experience to perform their designated research responsibilities.
- Provide ongoing oversight and supervision of research team members.
- Consider, disclose, and manage potential conflicts of interests related to the conduct of a research study in accordance with Federal and state regulations and institutional policy.

- Ensure the informed consent process is free from coercion or undue influence, has been voluntarily obtained, and has been properly documented.
- Ensure subject safety.
- Ensure subject privacy and confidentiality.
- Understand, comply with, and execute the data and safety monitoring plan.
- Be familiar with the proper use of an investigational product, as described in the protocol, in the current Investigator's Brochure, in a product information guide, and in other information sources provided by the sponsor.
- Maintain integrity of study records (*e.g.*, legible, accurate, complete, contemporaneous).

PIs are expected to submit the following to the IRB:

- Written requests for clarification if in question whether a project constitutes research or is QI.
- New study application (*e.g.*, exempt, expedited, convened IRB review); research may not commence until written IRB approval is provided.
- Request for modification to a previously approved or exempt study, including changes among the research team. A modification may not be initiated until IRB review occurs and written IRB approval is provided, except when necessary to eliminate apparent immediate hazards to a subject.
- A subject complaint.
- Continuing review application.
- Any internal or external audit or other monitoring findings.
- Notification of any change in study status, *e.g.*, closed to enrollment, sponsor suspension or termination of a study.
- SAE and/or unanticipated problem reports.
- Notification upon learning that a research subject has become incarcerated while participating in a study. all research interactions and involvement with, as well as obtaining identifiable private information about the incarcerated participant, must stop until the requirements of 21 CFR 56 and 45 CFR 46 Subpart C have been satisfied.
- Final reports and requests for termination.

18. Requirements for Unaffiliated Investigators

Unaffiliated investigators must comply with the CHA human subject protection education requirements or submit the completion certificate of the education program approved at his/her home institution with

verification of the institution's education program. If the unaffiliated investigator has not met the CHA requirements, the IRB Chair or designee will review the submitted documents for equivalence. If not deemed equivalent, the unaffiliated investigator will need to complete the CHA requirements.

In addition, an unaffiliated investigator must supply the current IRB approval of his or her home institution, if applicable.

Investigators who are not affiliated with CHA may engage in on-site human research activities only if a member of the professional or medical staff agrees to be his/her institutional sponsor and the unaffiliated individual has met the applicable institutional requirements (*e.g.*, Massachusetts Criminal Offender Record Information report, tuberculosis testing). The institutional sponsor must also provide a letter of support stating that s/he will oversee the on-site activities and provide a description of his/her role in the conduct of the study.

19. Health Insurance Portability and Accountability Act (HIPAA)

The HIPAA Privacy Office maintains specific policies addressing HIPAA in the research context.

Please also refer to CHA policy A-COM-0004 (Informed Consent for Research and Authorization for the Use and Disclosure of Protected Health Information) for information about the application of HIPAA in human research at CHA.

D. Other

Documents and Forms

The following is a list of intake forms used by the CHA IRB and a brief description of each form/its purpose:

Exempt Status Application	IRB intake form for a new minimal risk study that qualifies for exemption.
Expedited Review Application	IRB intake form for a new minimal risk study that qualifies for expedited review.
Convened IRB Review Application	IRB intake form for a new greater than minimal risk study.
Conflict of Interest Form	To be submitted with all new study applications and continuing review applications.
Department Review Form	Required for all new greater than minimal risk studies; for new minimal risk studies to be submitted at the discretion of the Department Chair.
Modification to an Existing Protocol	To be submitted when a protocol amendment or revision is made to a previously approved study.

Continuing Review or Termination Form	Required form to be submitted in order for a previously approved expedited or greater than minimal risk study to undergo continuing review (per 45 CFR 46.109, 46.110) OR when a study has been completed and the PI seeks to terminate the study.
Serious Adverse Event Reporting Form	Required form to be submitted when a SAE is being reported.

IRB forms are available on the IRB website; they are updated and revised, as needed.

IRB forms and correspondence submitted to the IRB office are to be signed and dated by the PI; signature stamps and electronic signatures may not be accepted. A co-Investigator may sign the submitted documents instead of the PI only if the PI is unavailable (*e.g.* leave of absence, illness).

Upon receipt of an application for review, the IRB office will pre-review the application per internal procedures. The PI or research team may be contacted if any required material is missing or if the forms have not been completed accurately or entirely.

The materials and information requested by the IRB are necessary to enable a thorough review of the research proposal in conformity with applicable laws, regulations, and Federal guidance.

Documents for Initial Review by IRB members

The primary reviewer of an initially submitted study will have a copy of the following documents prior to the convened IRB meeting:

- Required applicable IRB Forms and supporting documentation
- Protocol; for DHHS-supported multicenter clinical studies, the IRB should receive and review a copy of the DHHS-approved sample ICF(s) and the complete DHHS-approved protocol, if they exist.
- ICF(s)
- Investigator's Brochure, device information, *etc.*, if applicable
- A copy of the current FDA-approved package insert for approved drugs, scientific articles, MSDS sheets, *etc.*, if applicable, device user manual/operating manual, *etc.*, as applicable
- All materials provided to subjects including, but not limited to, telephone scripts, interview text, questionnaires, survey instruments, advertisements and letters, *etc.*, as necessary and if applicable.
- Recruitment materials (letters, advertisements, postings, e-mail announcements, *etc.*), if applicable.
- Any instruction sheet(s), informational sheet(s), contact letter(s), as required.
- COI form(s).

- HIPAA documentation.

Documents Required for Continuing Review

- Continuing Review Form
- Protocol
- ICF(s)
- COI form(s)
- All materials provided to subjects including, but not limited to, telephone scripts, interview text, questionnaires, survey instruments, advertisements and cover letters, if applicable.
- Recruitment materials (letters, advertisements, postings, e-mail announcements, *etc.*), if applicable.
- HIPAA documentation.
- Any instruction sheet(s), informational sheet(s), contact letter(s), as required.
- One copy of the validated ICF(s) used to enroll subjects during the past year
- DSMB report, if applicable
- Summary of SAEs, if applicable

Documents for Continuing Review by IRB Members

Each IRB member who will attend the convened IRB meeting will receive a copy of the following minimum information prior to a study being presented to the convened IRB for continuing review:

- Continuing Review Form
- Protocol
- ICFs

Information Required for IRB Notification

If present from the prior month, each IRB member will receive notification of the following events in a monthly compilation:

- Studies Granted Exempt Status
- Expedited Initial Review Approval
- Expedited Continuing Review Approval
- Expedited Modification Approval
- Emergency Use Review

- Non-compliance
- Involuntary Suspension or Terminations
- Any event deemed reportable to a regulatory Department of Agency
- Any other information as deemed necessary by the IRB Chair.

Proposed Changes to Protocol and/or ICF: Change to a Protocol Previously Approved

- PI's request for amendment, including a detailed description of the proposed change and an explanation of the rationale for the modification.
- Revised protocol and ICF(s), as applicable.
- One copy of the tracked and untracked revised document, including an updated version date or number.

In addition to the above, the Reviewer should have a copy of the following:

- Protocol
- ICF(s)
- Any additional supporting information pertinent to the proposed change such as information supplied by the study sponsor, articles published in the primary literature, *etc.*

SUMMARY OF REVISIONS

Issue	Section of document revised
01 August 2012 Operations Manual created as 1 document	
18 December 2012 Added Harvard Catalyst Information	Introduction, E6: Harvard Catalyst
12 June 2014	
• Updated adverse event and unanticipated problem reporting	Unanticipated Problem and Adverse Event Reporting
• Revised "CHA Translation Services" to "Multicultural Affairs and Patient Services"	Translation of Study Documents
• Formatting and typographical errors corrected	Throughout document
• Updated acronyms	Abbreviations
14 July 2014 Updated informed consent and HIPAA-research policy	Informed Consent
25 February 2015	

New policy (Application of Additional Regulations Depending on Federal Funding) added. Policy voted on and approved by the convened IRB 02/25/15.	New section added
24 April 2015 Removed co-Chair references, added Vice Chair; minor corrections/updates/clarifications/typographical adjustments, including in-office expedited notifications sent prior to next meeting in the event an IRB meeting is cancelled.	Throughout document
16 December 2015 Corrected page numbers in TOC. Updated document not sent to the convened IRB for review or vote as content changes were not made.	Table of Contents
07 December 2016 Updated responsibilities to more accurately reflect current roles and responsibilities of staff and IRB members (*e.g.*, in-office expedited review of materials, Secondary Reviewer).	Throughout document
07 March 2017 Updated url references (*e.g.*, OHRP, FDA) related to IRB meetings convened via telephone conference call.	Quorum of the IRB
Updated HUD information based on 21st Century Cures Act	Humanitarian Use Device
22 December 2017 Updates made based on 2018 New Final Rule; other general updates made, including typographical and grammatical corrections, reorganization of information, updates made to referenced regulations, wording clarifications and refinements.	Throughout document