



National Cancer Institute

Central Institutional Review Board

Standard Operating Procedures

CIRB Standard Operating Procedures

*Additional copies are available from the CIRB website (<http://www.ncicirb.org>)
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Current as of January 21, 2019

The NCI CIRB Initiative is based in the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

Mission of the CIRB Initiative

The NCI Central Institutional Review Board is dedicated to protecting the rights and welfare of participants in cancer clinical trials. Institutions across the country rely on our national experts to ensure that clinical trials are reviewed efficiently and with the highest ethical and quality standards. We play a critical role in helping the National Cancer Institute accelerate scientific discovery and improve cancer prevention, treatment and care.

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Section 1.0 Introduction

1.1 History

1.1.1 The Armitage Report Recommendation

In 1996, the National Cancer Institute (NCI) Clinical Trials Program Review Group was tasked with addressing the challenge of responding to expanding opportunities of new therapeutics and technology while reducing costs of research through efficiencies. The Review Group met six times over an 11-month period and its recommendations, known as “The Armitage Report,” included establishing a “streamlined IRB process” for multi-center trials such as those coordinated by the NCI’s Clinical Trials Cooperative Group Program. The Armitage Report is located at the following URL:

http://deainfo.nci.nih.gov/advisory/bsa/bsa_program/bsactprgmin.pdf

Due to the importance of investigators from multiple sites using a single version of a protocol, local IRBs reviewing Cooperative Group trials could not make any changes in the protocol and were restricted to approving the protocol supplied by the Cooperative Group or not approving the study for participation at their institution. This situation resulted in redundant reviews across the nation as local IRBs reviewed the same protocol without the ability to effect changes that could potentially improve study participant protections.

In response to the Armitage Report’s recommendation to streamline the IRB process, the NCI worked in conjunction with the Office for Protection from Research Risks (OPRR), now known as the Office for Human Research Protections (OHRP), and the Food and Drug Administration (FDA) to create the Central Institutional Review Board (CIRB) Initiative. The CIRB Initiative would create a more effective and efficient clinical research effort by conducting a full, board review centrally, thus eliminating redundant processes.

1.1.2 Support for Central Review

The two primary regulatory bodies overseeing human subject protection programs, OHRP and FDA, have publicly supported central review. Quoting from a recent OHRP Request for Information, “If institutions become more willing to rely on cooperative review arrangements and on review of IRBs operated by other institutions or organizations, OHRP believes that this will reduce administrative burdens associated with implementing 45 CFR 46 without diminishing human subject protections.”

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Additionally, SACHRP, the Secretary’s Advisory Committee on Human Research Protections has endorsed central review in a letter to the Secretary of Health and Human Services located at the following URL: <http://www.hhs.gov/ohrp/sachrp/sachrletter091808.html>.

The FDA supports central review by regulation in 21 CFR 56.114, “...institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.”

The FDA has also issued guidance in support of centralized review titled “Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials” located at the following URL: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm>.

1.2 Operating Structure

There are four CIRBs: the Adult CIRB – Late Phase Emphasis and the Adult CIRB – Early Phase Emphasis meet twice a month; the Pediatric CIRB and Cancer Prevention and Control (CPC) CIRB meet monthly. The Adult CIRB – Late Phase Emphasis OHRP registration number is IRB00000781. The Adult CIRB – Early Phase Emphasis OHRP registration number is IRB00009430. The Pediatric CIRB OHRP registration number is IRB00004296. The CPC CIRB OHRP registration number is IRB00010018. Per OHRP’s direction, the NCI CIRB does not hold an FWA because it is not the entity conducting the research. The Institutional Official for the CIRB is the Director of the NCI’s Division of Cancer Treatment and Diagnosis (DCTD).

The CIRB Initiative is led by NCI employees based in the Cancer Therapy Evaluation Program (CTEP) of DCTD and in the Division of Cancer Prevention. The CIRB Operations Office is supported by contractor staff responsible for the following:

1. Managing and supporting all CIRB operations;
2. Recruiting and enrolling new institutions;
3. Supporting the enrolled institutions;
4. Maintaining and updating the CIRB website; and
5. Providing the IT infrastructure to securely maintain all data.

All institutions with FWAs currently conducting CIRB-approved studies at their institutions are eligible to join the CIRB Initiative.

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1.3 Establishing Local Context

The CIRB is informed of local context considerations via submission of three worksheets. First, the Annual Signatory Institution Worksheet providing local context considerations for the signatory institutions as well as any component or affiliate institutions. Second, the Annual Principal Investigator Worksheet providing local context considerations relative to the PI within the institutional context. Third, the Principal Investigator submits the Study-Specific Worksheet to open a study with the CIRB in light of the local context considerations provided in the two previous worksheets.

1.4 2018 Common Rule Requirements

The CIRB adopted the 2018 Common Rule Requirements on January 21, 2019. The implementation of the 2018 Requirements include the following:

- a. All studies approved or approved pending modification prior to January 21, 2019 operate under the pre-2018 Requirements.
- b. All studies approved after January 21, 2019 operate under the 2018 Requirements.
- c. The CIRB is not going to transition any studies operating under the pre-2018 Requirements to the 2018 Requirements. These studies should remain under the pre-2018 Requirements throughout the life of the study.
- d. References within this document have been updated to include pre-2018 Requirements, 2018 Requirements, and FDA references when appropriate. If references are not identified as pre-2018 Requirements and 2018 Requirements, the reference did not change between versions.
- e. Continuing reviews will continue to be conducted for all studies because of the requirement to comply with FDA regulations for most of the CIRB studies.
- f. For any review that would require limited IRB review, the CIRB will follow the expedited review process.

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Section 2.0 Foundational Principles

2.1 Institutional Authority

2.1.1 The CIRB has authority to approve, require modifications of (to secure approval), or disapprove research activities involving human subjects. For studies approved after January 21, 2019 this includes exempt research activities under §46.104 for which limited IRB review is a condition of exemption (under §46.104(d)(2)(iii), (d)(3)(i)(c), and (d)(7), and (8)). The CIRB also has the authority to suspend or terminate approval of research not being conducted in accordance with CIRB or regulatory requirements, or that has been associated with unexpected serious harm to study participants. The regulatory basis for this authority is as follows:

2.1.1.1 For research that is not FDA regulated, Department of Health and Human Services (DHHS) regulations pertaining to rights and welfare of subjects (45 CFR 46)

[\[http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html\]](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html).

2.1.1.2 For research that is regulated by the U.S. Food and Drug Administration (FDA), FDA regulations pertaining to rights and welfare of subjects participating in research involving investigational drugs, devices, or biologics (21 CFR 50 and 21 CFR 56) in addition to the regulations in 45 CFR 46.

[\[https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50,](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50)
[https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56\]](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56).

2.1.2 Each Signatory Institution grants authority to the CIRB when the Signatory Institution’s Institutional Official and the Institutional Official for the CIRB sign the Authorization Agreement and the Office for Human Research Protections has accepted an FWA designating the CIRB as an IRB for that institution under Item #6 “Designation of Institutional Review Boards” located at the following URL:

<http://www.hhs.gov/ohrp/assurances/forms/fwainstructions.html>

2.1.2.1 The Signatory Institution retains the authority to observe, or have a third party observe, the consent process and the conduct of the research. The CIRB has the authority to direct this be done when necessary.

2.1.3 The NCI CTEP Human Research Protection Program (HRPP) components are: an HRPP organizational official (Institutional Official for the CIRB);

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CTEP, DCP, and their component Branches; CIRBs; CIRB Operations Office; Study Chairs; and participating institutions including the signatory official, Principal Investigators, and research staff.

2.1.4 The Institutional Official for the CIRB has the ultimate responsibility for oversight and funding of the HRPP and related activities. The Institutional Official for the CIRB fulfills program management responsibilities which broadly encompass the scientific and fiscal management and monitoring of activities supported by the HRPP. These responsibilities relative to the DCP component of the HRPP are delegated to the Associate Director, DCP. The Institutional Official’s responsibilities are to:

2.1.4.1 Oversee scientific and personnel administration of the CTEP HRPP;

2.1.4.2 Interview and select key professional personnel, furnish leadership and coordination of effort so that maximum potential of the staff will be realized in meeting the goals and objectives of CTEP;

2.1.4.3 Provide overall executive direction and scientific leadership to CTEP Branch Chiefs and other senior staff members;

2.1.4.4 Establish goals, operational plans, and scientific program direction for the HRPP, project CTEP staffing needs and space, recruit qualified staff, and delegate responsibility and authority as appropriate to the qualifications of personnel;

2.1.4.5 Assure that all scientific, fiscal, and administrative responsibilities are met in a timely and well-documented fashion;

2.1.4.6 Project the annual operating budget for the HRPP and determine and oversee the allocation of approved resources;

2.1.4.7 Assure that the HRPP staff has adequate knowledge of operating policies and procedures as well as Federal regulations which govern the Program’s HRPP’s activities;

2.1.4.8 Meet regularly with all CTEP Branch Chiefs and the Head, CIRB Initiative; Head, CIRB Strategy and Operations; and DCP Liaison and other appropriate DCP representatives to assure that their project budgets are sufficient to support the needs of the clinical research they support through CIRB review;

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2.1.4.9 Change priorities to cover new emergent needs so that clinical trials and study participant safety therein are never compromised for lack of resources;

2.1.4.10 Meet routinely with the Head, CIRB Initiative; Head, CIRB Strategy and Operations; and DCP Liaison to assure that the CIRB has policies in place to handle conflict of interest;

2.1.4.11 Provide access to NCI legal counsel should a situation arise that requires legal input; and

2.1.4.12 Oversee, in collaboration with the Head, CIRB Initiative; Head, CIRB Strategy and Operations; and DCP Liaison the quality improvement plan for the CIRB, the HRPP education program, and outreach.

2.1.5 The CIRB acts in compliance with the Federal regulations cited in section 2.1.1 and follows the policies and procedures outlined in this document.

2.1.5.1 Based on compliance with the regulations cited in section 2.1.1, all amendments to previously approved research are reviewed by the CIRB and all amendments require CIRB approval before activation except for changes implemented prior to CIRB approval in order to eliminate apparent immediate hazards to the subjects as permitted by 45 CFR 46.103(b)(4)(iii) under pre-2018 Requirements, 45 CFR 46.108(a)(3)(iii) under 2018 Requirements, and 21 CFR 56.108(a)(4) for FDA-regulated studies.

2.2 Statement of Ethical Principles

The CIRB and the components of the HRPP are guided by the ethical principles governing research involving humans as subjects as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, entitled The Belmont Report Ethical Principles and Guidelines for the Protection of Human Subjects of Research located at the following URL: <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>. All individuals in the HRPP (Study Chairs, Principal Investigators, and research staff, CIRB members and chairs, CIRB Operations Office staff, the Organizational Official, and all other employees of the HRPP) are expected to comply with these ethical principles.

2.3 Scope of Review Activities

2.3.1 All NCI-sponsored research is under the jurisdiction of OHRP and, when applicable, the FDA.

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2.3.1.1 *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to general knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For research approved prior to January 21, 2019, the following definitions are applied:

2.3.1.1.1 Systematic investigation: Use of a predefined plan to collect and analyze information to increase understanding.

2.3.1.1.2 Generalizable knowledge: Information attained from systemic investigation.

2.3.1.2 The following activities reviewed after January 21, 2019 are deemed not to be research:

2.3.1.2.1 Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

2.3.1.2.2 Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

2.3.1.2.3 Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

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2.3.1.2.4 Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

2.3.1.2 *Research* as defined by FDA regulations means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505 (i) or 520 (g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations.

2.3.1.3 *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research:

(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

(ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

2.3.1.3.1 *Intervention* includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.

2.3.1.3.2 *Interaction* includes communication or interpersonal contact between investigator and subject.

2.3.1.3.3 *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

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2.3.1.3.4 *Identifiable private information* is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

2.3.1.3.5 An *identifiable biospecimen* is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

2.3.1.4 *Human subject* as defined by FDA regulations means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject might be either a healthy individual or a patient. For research involving medical devices a human subject is also an individual on whose specimen an investigational device is used. When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects.

2.3.2 The CIRB only reviews selected NCI-sponsored trials.

2.3.2.1 The Study Chair is the CIRB’s point of contact and is responsible for all study activities.

2.3.2.2 NCI reviews and approves all studies before submission to the CIRB for review.

2.3.2.3 If the CIRB disapproves a study on initial review, CIRB representatives meet with NCI staff, the Institutional Official for the CIRB and the Study Chair to resolve the CIRB’s concerns.

2.3.2.4 Officials of the NCI may not approve research for which the CIRB is an IRB of record unless it has been approved by the CIRB.

2.3.3 The Adult CIRB – Late Phase Emphasis reviews all NCI-sponsored Phase 3 Adult clinical trials. The CIRB may review other studies upon request from CTEP.

2.3.4 The Adult CIRB – Early Phase Emphasis reviews clinical trials sponsored by the Experimental Therapeutics Clinical Trials Network (ETCTN), the Adult Brain Tumor Consortium (ABTC), and Cancer Immunotherapy Trials Network (CITN). The CIRB may review other early phase studies upon request from CTEP.

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2.3.5 The Pediatric CIRB reviews all NCI-sponsored Pilot, Phase 1, Phase 2, and Phase 3 Children’s Oncology Group clinical trials and the Pediatric Brain Tumor Consortium (PBTC). The CIRB may review other studies upon request from CTEP.

2.3.6 The CPC CIRB reviews all cancer prevention and control protocols sponsored by the NCI Division of Cancer Prevention (DCP) and conducted through the NCORP, DCP Phase I Consortia program, and the NCI Division of Cancer Control and Population Sciences (DCCPS) Cancer Care and Delivery Research (CCDR) program. The CIRB may review other studies upon request from DCP.

2.3.7 Ancillary/Companion Studies are reviewed by the CIRB when the main treatment study is approved by the CIRB. The CIRB may review other ancillary/companion studies upon request.

2.3.8 Limits to Scope of Review

2.3.8.1 The CIRB is not constituted to review research for inclusion of prisoners.

2.3.8.2 The CIRB does not review the following:

- 2.3.8.2.1 Research conducted under the exception to the requirement for informed consent for emergency research described in Federal regulation FDA 21 CFR 50.24;
- 2.3.8.2.2 Reports of emergency use of a test article as described in Federal regulations 21 CFR 56.102(d), 56.104(c), and 312.36 or the use of a test article without informed consent as outlined in Federal regulation 21 CFR 50.23;
- 2.3.8.2.3 HIPAA authorization language or requests for waivers of HIPAA authorization.
- 2.3.8.2.4 Transnational research.

2.3.8.3 The CIRB’s review of a study does not extend to review and approval of the coordinating group’s or lead organization’s engagement in human subjects research as, for example, data/statistical coordinating center or biospecimen repository.

2.4 Definition of Term “CIRB”

In this document the acronym “CIRB” refers to all four CIRBs. References to individual CIRBs will be made using their individual name.

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Section 3.0 Division of Responsibilities

3.1 CIRB Responsibilities

The responsibilities of the CIRB and the Signatory Institution are detailed in the Authorization Agreement/Division of Responsibilities located at the following URL: <https://www.ncicirb.org/institutions/becomingsignatoryinstitution>. The Authorization Agreement is signed by the Signatory Institution’s Signatory Official and the Signatory Official for the CIRB during enrollment of the Signatory Institution and is required for the Signatory Institution to participate in the CIRB.

3.1.1 The responsibilities of the CIRB are to:

3.1.1.1 Maintain an NCI CIRB membership that satisfies the requirements of 45 CFR 46 and 21 CFR 56 and provides special expertise as needed to adequately assess all aspects of each study;

3.1.1.1.1 Post the roster of NCI CIRB membership on the NCI CIRB website.

3.1.1.2 Conduct initial, amendment, and continuing review of studies as well as review of any other study-specific documents submitted by the Study Chair to the CIRB.

3.1.1.3 Conduct review of local context considerations as outlined in the following Worksheets:

3.1.1.3.1 Annual Signatory Institution Worksheet;

3.1.1.3.2 Annual Principal Investigator Worksheet; and

3.1.1.3.3 Study-Specific Worksheet.

3.1.1.4 Conduct review of potential unanticipated problems and/or serious or continuing noncompliance when the Signatory Institution, Signatory Institution Principle Investigator, or other entity reports an incident, experience, or outcome to the CIRB;

3.1.1.4.1 This review includes reporting any unanticipated problem and/or serious or continuing noncompliance determination to OHRP, the FDA, and the Signatory Official for the CIRB. Reporting to the Signatory Official for the CIRB satisfies the requirement for notification of the department or agency head as required by 45 CFR 46.103(b)(5) under pre-2018

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Requirements and 45 CFR 46.108(a)(4) under 2018 Requirements.

- 3.1.1.5 Report any suspension or termination of CIRB approval to OHRP, FDA, and the Signatory Official for the CIRB. Reporting to the Signatory Official for the CIRB satisfies the requirement for notification of the department or agency head as required by 45 CFR 46.113;
- 3.1.1.6 Conduct review of individual Adverse Event Reports for studies without a Data and Safety Monitoring Board (DSMB) or sufficient monitoring plan;
- 3.1.1.7 Notify participating Investigators of CIRB determinations by posting all study-wide documents related to CIRB reviews and decisions to a secure website and notify research staff and institutional designees of the postings.
- 3.1.1.8 Provide institution-specific documents related to CIRB reviews via email to research staff and institutional designees;
- 3.1.1.9 Notify the Signatory Institution immediately if there is ever a suspension or restriction of the CIRB’s authorization to review a study; and
- 3.1.1.10 Post the NCI CIRB Standard Operating Procedures on the CIRB website.

3.2 Signatory Institution Responsibilities

- 3.2.1 The responsibilities of the Signatory Institution are to:
 - 3.2.1.1 Comply with the CIRB’s requirements and directives;
 - 3.2.1.2 Report to the CIRB the names of any Component or Affiliate Institutions that meet the following definitions:
 - 3.2.1.2.1 Component Institutions are defined by the CIRB as meeting all of the following criteria:
 - a) The Component Institution operates under a different name than the Signatory Institution, but the Signatory Institution has legal authority for the Component Institution;

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- b) The FWA number for the Component Institution is the same as the Signatory Institution;
- c) The local context considerations of the Component Institution are the same as the Signatory Institution;
- d) The boilerplate language and institutional requirements of the Component Institution are the same as the Signatory Institution; and
- e) The conduct of research at the Component Institution is monitored by the same office as the Signatory Institution.

3.2.1.2.2 Affiliate Institutions are defined by the CIRB as meeting all of the following criteria:

- a) The local context considerations of the Affiliate Institution are the same as the Signatory Institution.
- b) The boilerplate language and institutional requirements of the Affiliate Institution are the same as the Signatory Institution; and
- c) The conduct of research at the Affiliate Institution is monitored by the same office as the Signatory Institution.

3.2.1.3 Ensure the safe and appropriate performance of the research at the Signatory Institution and at all Components and Affiliates. This includes, but is not limited to:

- 3.2.1.3.1 Ensuring the initial and ongoing qualifications of investigators and research staff;
- 3.2.1.3.2 Ensuring adequate resources to perform the research including proper facilities and equipment to conduct research procedures.
- 3.2.1.3.3 Overseeing the conduct of the research;
- 3.2.1.3.4 Monitoring protocol compliance;
- 3.2.1.3.5 Maintaining compliance with state, local, or institutional requirements related to the protection of human subjects. When in conflict with CIRB determinations, the most restrictive requirement applies;
- 3.2.1.3.6 Providing a mechanism to receive and address concerns from local study participants and others about the conduct of the research; and
- 3.2.1.3.7 Investigating, managing, and providing notification to the NCI CIRB of any study-specific incidence, experience, or outcome that appears to rise to the level of an unanticipated problem and/or serious or

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continuing noncompliance. When notifying the NCI CIRB of a potential unanticipated problem and/or serious or continuing noncompliance, the institution must provide a plan to manage the incident, experience, or outcome, including measures to prevent similar occurrences;

As part of ensuring safe and appropriate performance of research the Signatory Institution has the authority to observe any aspect of the research process including observing the consent process. The CIRB retains the authority to direct this to be done when necessary.

- 3.2.1.4 Provide updates in a timely manner to the NCI CIRB whenever a Signatory Institution Principal Investigator is replaced. The CIRB requires submission and approval of the Annual Principal Investigator Worksheet prior to finalizing the replacement Principal Investigator;
- 3.2.1.5 Notify the CIRB when a regulatory deficiency has been cited on an audit that occurred during the time that the CIRB was responsible for study review;
- 3.2.1.6 Complete and submit the Annual Signatory Institution Worksheet, the Annual Principal Investigator Worksheet, and any other worksheets/forms required by the CIRB for participation;
- 3.2.1.7 Have CIRB-approved Principal Investigators complete and submit the Study-Specific Worksheet to open a study;
- 3.2.1.8 Incorporate NCI CIRB-approved boilerplate language into the NCI CIRB-approved model consent form to create the consent form to use for a specific study:
 - 3.2.1.8.1 Make no language changes to the consent form with the exception of CIRB-approved boilerplate language;
 - 3.2.1.8.2 Obtain CIRB approval of changes to the boilerplate language prior to implementation; and
 - 3.2.1.8.3 Obtain CIRB approval of translations of the consent form prior to implementation;
- 3.2.1.9 Maintain a regulatory file for each study under CIRB purview as per local institution and sponsor policy; and

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3.2.1.10 Conduct full board review of any study enrolling prisoners, since the NCI CIRB is not constituted to review studies enrolling prisoners.

3.3 Further Delineation of Responsibilities by Topic

3.3.1 Assent (for pediatric trials)

The CIRB makes the determination whether assent of the child is required. Local institutional policy regarding whether and how to document assent is provided as part of the local context considerations.

3.3.2 HIPAA

Compliance with HIPAA regulations is considered an institutional requirement and remain the purview of the local institution. The CIRB does not permit HIPAA language to be included as boilerplate language. HIPAA requirements must be addressed by the institution in a separate document.

3.3.3 Individual with Impaired Decision-Making Capacity

The CIRB determines whether individuals with impaired decision-making capacity as a category are eligible for a study. The local institution provides the details regarding state law and institutional policy regarding the authority of legal guardians to consent to research, as well as documentation of proxy consent as part of the local context considerations.

3.3.4 Prisoners

The CIRB is not constituted to review studies eligible for prisoners, per 45 CFR 46 Subpart C, so cannot be the IRB of Record if the local investigator wants to enroll a prisoner or if a study participant becomes incarcerated during the course of the study. If the local investigator wants to enroll prisoners on a particular study, or if a study participant becomes incarcerated during the course of the study, the local IRB must conduct a full board review of that study per Federal regulations.

3.3.5 Other Committee Reviews

The CIRB’s review is designed to meet the requirements for review by an Institutional Review Board (IRB). Requirements for review by other committees such as a Radiation Safety Committee or Institutional Biosafety Committee are the responsibility of the local institution.

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Section 4.0 CIRB Membership

4.1 Organization

4.1.1 All members of the CIRB are regular members. Members of one CIRB may serve as subject matter consultants for another CIRB. The CIRB may use unaffiliated subject matter consultants for a specific review if requested by the Chair. Patient advocates serving as non-scientists on one CIRB serve as alternates for patient advocates serving as non-scientists on all other CIRBs.

4.1.2 Each CIRB meets the following requirements:

4.1.2.1 Each CIRB has at least five members with varying backgrounds to promote complete and adequate review of research commonly conducted by the organization.

4.1.2.2 No CIRB has members who represent a single profession.

4.1.2.3 Each CIRB has at least one member whose primary concerns are in scientific areas.

4.1.2.4 Each CIRB has at least one member whose primary concerns are in nonscientific areas.

4.1.2.5 Each CIRB has at least one member who is not otherwise affiliated with the organization and who is not part of the immediate family of a person who is affiliated with the organization.

4.1.2.6 Each CIRB has at least one member who represents the perspective of research participants.

4.1.3 Each CIRB has a Chair and may have one or more Vice Chair(s).

4.1.4 Each CIRB may have up to three subcommittees: the CIRB Adverse Event Subcommittee, the Conflict of Interest Subcommittee, and the CIRB Local Context Subcommittee.

4.2 Qualification of Members

4.2.1 The membership of the CIRB may include patient advocates; medical, surgical, and radiation therapy oncologists; ethicists; non-physician healthcare providers (oncology nurses and pharmacists); statisticians; and

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others as deemed appropriate to provide a high-quality review. NCI will appoint members, including Chairs and Vice Chairs, to meet the specific requirements of 45 CFR 46.107 so that the membership is sufficiently qualified through expertise, experience, and diversity to ensure its ability to safeguard the rights and welfare of human subjects.

- 4.2.2 All CIRB members demonstrate and maintain sufficient knowledge of the ethical principles and Federal requirements for protecting research participants. All CIRB members are committed to the principles of human subject protections. The CIRB members, as a Board, are qualified to ascertain the acceptability of the research in terms of Federal regulations and standards of professional conduct and practice.
- 4.2.3 CIRB members who have a conflict of interest with a study as defined by the Conflict of Interest Policy for CIRB Members do not participate in the final deliberations and votes on proposed research or continuing review of previously approved research including review of unanticipated problems, adverse events, changes in research, and serious or continuous noncompliance. CIRB members with a conflict of interest do not perform expedited reviews of research with which the member has disclosed a conflict. CIRB Members with a conflict of interest with a study do not count towards quorum for the review of that study.
- 4.2.4 An employee of the NCI cannot be appointed to serve as a member of the CIRB.
- 4.2.5 Each CIRB member must be available to regularly attend CIRB meetings and be willing to dependably fulfill the responsibilities of a primary reviewer when assigned.
- 4.2.6 Each CIRB member must agree to have his/her full name, profession, and affiliations made public.
- 4.2.7 All CIRB members must agree to keep deliberations and actions of the CIRB confidential.
- 4.3 Selection and Appointment
 - 4.3.1 The NCI solicits names for appointments from a variety of sources (e.g., cancer advocacy groups, coordinating groups, current and former CIRB rosters, Federal agencies, professional organizations, and self-nomination). The names of persons in ethics, healthcare, or advocacy who have demonstrated expertise, experience, and interest regarding the protection of the rights and welfare of study participants are considered for appointment.

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- 4.3.2 When selecting members, consideration is given to assuring appropriate diversity by profession, ethnic background, and gender, and to include both non-scientific and scientific members. Consideration is also given to representation of vulnerable populations.
- 4.3.3 CIRB members are volunteers and are typically appointed for a two-year term. A member may continue to serve beyond two years if recommended by the Head of the CIRB Initiative.
- 4.3.4 At the request of the Head of the CIRB Initiative, the Chair may be asked to evaluate the knowledge and skills of the members scheduled for continuation. If at any time the Chair determines the member does not demonstrate appropriate knowledge and skill, the Chair may recommend additional training or may recommend that the member not continue to serve on the CIRB.
- 4.3.5 CIRB members are evaluated annually by the Head of the CIRB Initiative to determine if the member continues to meet the responsibilities of membership. An evaluation letter, accompanied by an individualized Meeting Attendance Report, is provided to the Chair, Vice Chair, and CIRB members that document their meeting attendance and reviews completed in the last year. CIRB members may be required to complete additional training, to correct an identified deficiency, or be removed from the CIRB, if additional educational efforts are unsuccessful or the member is unwilling to participate. This determination is made and communicated to the CIRB member by the Head, CIRB Initiative.
- 4.3.6 CIRB members may resign by notification to the Chair of their respective CIRB or to the Head, CIRB Initiative; the CIRB Contracting Officer Representative; or the CIRB Operations Office.
- 4.3.7 To encourage CIRB members to speak freely and to safeguard proprietary information, all CIRB members must sign a confidentiality agreement as a condition of serving on the CIRB.
- 4.3.8 Maintenance of the CIRB Membership Roster
 - 4.3.8.1 The membership roster for each CIRB is updated when changes occur.
 - 4.3.8.2 The following information is maintained for each member:
 - 4.3.8.2.1 Name;
 - 4.3.8.2.2 Sex and ethnicity;

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- 4.3.8.2.3 Degrees;
- 4.3.8.2.4 Representative capacity;
- 4.3.8.2.5 Indications of experience, such as board certifications, licenses, etc.;
- 4.3.8.2.6 Information sufficient to describe each member’s chief anticipated contributions to the CIRB deliberations; and
- 4.3.8.2.7 Any employment or other relationship between the member and the NCI.

4.4 Training of CIRB Members

- 4.4.1 New CIRB members participate in a telephone orientation session that covers the structure and mandate of the CIRB, the Belmont Report, and the applicable Federal regulations. Records of attendance at the telephone orientation session are maintained by the CIRB Operations Office.
- 4.4.2 New CIRB members are required to receive training on the internet-enhanced conference call system called ePanel[®] which is used for most CIRB meetings.
- 4.4.3 Each CIRB member is required to complete the Web-based modules on human subjects protections provided through the CITI Program and provide written verification of training completion to the CIRB Operations Office. The CITI training must be maintained with training occurring every two years.
- 4.4.4 New CIRB members will be provided with the following:
 - 4.4.4.1 CIRB Orientation Packet;
 - 4.4.4.2 CIRB Standard Operating Procedures;
 - 4.4.4.3 Institutional Review Board Member Handbook, R.J. Amdur (Ed.) and;
 - 4.4.4.4 Any other related materials deemed necessary by the Head, CIRB Initiative; the CIRB Contracting Officer Representative; and the CIRB Operations Office.
- 4.4.5 New CIRB members observe at least one CIRB meeting before serving on the CIRB unless the members are to serve on a new CIRB which has not yet met.

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- 4.4.6 New CIRB members cannot serve on the CIRB until all training requirements have been completed.
- 4.4.7 All CIRB members are invited to attend in-person training and education sessions when arranged by the NCI and the CIRB Operations Office. Content and attendance is appropriately documented. Regular attendance is expected. CIRB members who cannot attend will be provided with materials to review. The training sessions may also include presentations on special topics that are intended to provide the CIRB members a better understanding of NCI-sponsored clinical trial development and management processes, regulatory issues, or current topics of debate in IRB forums. Topics may include ethical, scientific, and/or operational issues.
- 4.4.8 The Chairs of each CIRB consider the training needs of their respective members and may suggest appropriate topics for training.
- 4.4.9 The CIRB Operations Office monitors recent developments in ethics and research and distributes information to CIRB members on an ongoing basis to keep the CIRB informed of current events.
- 4.4.10 Special training sessions are scheduled by the CIRB Operations Office and held as needed.
- 4.4.11 Training may also occur during convened CIRB meetings, when appropriate.
- 4.4.12 The CIRB Operations Office tracks all training for CIRB members.
- 4.5 Attendance Requirements
 - 4.5.1 CIRB members are expected to attend all CIRB meetings.
- 4.6 Appointment and Duties of the Chair and Vice Chair
 - 4.6.1 The Chair and Vice Chair of each CIRB is appointed by the Head, CIRB Initiative for a term of two years.
 - 4.6.2 The CIRB Chair is a voting member of the CIRB and presides over each CIRB meeting.
 - 4.6.3 If the Chair is absent, the CIRB Vice Chair serves as the acting Chair and assumes all responsibilities and obligations of the Chair. In the event neither the Chair nor the Vice Chair is available to preside over a specific

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meeting, the Chair will designate another CIRB member of the CIRB to serve as the acting Chair for that meeting.

4.6.4 The following are responsibilities of the Chair:

- 4.6.4.1 Remain knowledgeable of the ethical, legal, and regulatory issues applicable to studies and consent documents reviewed by the CIRB;
- 4.6.4.2 As appropriate, participate in the development of CIRB meeting agendas, policies, and procedures;
- 4.6.4.3 Confirm appropriateness of reviewer assignments for the CIRB meeting;
- 4.6.4.4 Review all studies presented to the convened CIRB and communicate with other reviewers as needed so that important IRB issues may be resolved or identified prior to the convened meeting;
- 4.6.4.5 Attend CIRB meetings via teleconference and ePanel[®];
- 4.6.4.6 Direct the proceedings and discussion of convened CIRB meetings by keeping the dialogue focused on important IRB issues and ensuring that the meeting process is both efficient and effective;
- 4.6.4.7 Provide the tie-breaking vote when necessary, otherwise the Chair does not vote;
- 4.6.4.8 Adhere to and administer CIRB decisions;
- 4.6.4.9 Respond to the CIRB Operations Office in a timely manner with regard to CIRB correspondence and processes;
- 4.6.4.10 Review and provide a timely determination on requests that meet the Federally-defined criteria for expedited review or delegate the authority to do so;
- 4.6.4.11 Review CIRB correspondence representing CIRB’s decisions in a timely fashion or delegate the authority to do so;
- 4.6.4.12 Work with the CIRB Operations Office to maintain efficient and effective administrative processes;

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- 4.6.4.13 As appropriate, participate in the resolution of controversial substantive or procedural matters;
- 4.6.4.14 Represent the CIRB in discussing CIRB decisions with Study Chairs and/or the Cooperative Groups;
- 4.6.4.15 Notify NCI of invitations to speak on behalf of, or about, the NCI CIRB Initiative.
- 4.6.4.16 Communicate regularly with the Head, CIRB Initiative, CIRB Contracting Officer Representative, and CIRB Operations Office; and
- 4.6.4.17 Consider the training needs of the CIRB members and suggest appropriate topics for training.
- 4.6.5 It is recommended that Chairs and Vice Chairs attend IRB-related educational conferences or forums at least once a year in addition to CIRB-specific Education Day(s).
- 4.6.6 In the event the Chair is unable to fulfill these responsibilities, the Vice Chair assumes all responsibilities of the Chair until the NCI appoints a replacement CIRB Chair.
- 4.6.7 On an ongoing basis, the Head of the CIRB Initiative monitors the Chair’s and the Vice Chair’s performance with respect to knowledge of and compliance with regulations and CIRB Standard Operating Procedures. If the Chair or Vice Chair performance reflects an inadequate knowledge or lack of compliance with applicable regulations and Standard Operating Procedures, the Chair or Vice Chair will be given an opportunity to correct the deficiencies or a replacement Chair or Vice Chair will be appointed.

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4.7 Duties of CIRB Members

4.7.1 CIRB members are responsible for the following:

- 4.7.1.1 Attend regularly scheduled CIRB meetings via teleconference and ePanel[®];
- 4.7.1.2 Understand the CIRB Conflict of Interest policy and disclose potential or known conflicts of interest;
- 4.7.1.3 Review all materials received and/or electronically posted prior to the meetings;
- 4.7.1.4 Serve as primary reviewers for scheduled reviews when assigned, and submit a timely written review of the assigned study using the appropriate reviewer form;
- 4.7.1.5 Participate in discussions and vote at CIRB meetings;
- 4.7.1.6 Maintain confidentiality of CIRB discussions and all meeting material;
- 4.7.1.7 Maintain knowledge of regulations and policies pertaining to human research; and
- 4.7.1.8 Maintain knowledge of CIRB policies pertaining to CIRB-decision making.
- 4.7.1.9 Notify NCI of invitations to speak on behalf of, or about, the NCI CIRB Initiative.

4.8 Primary Reviewer

4.8.1 The CIRB uses a primary reviewer system.

- 4.8.1.1 Two reviewers (one scientific and one non-scientific) are required to review the materials for initial reviews.
- 4.8.1.2 One CIRB member, with appropriate expertise and qualifications, serves as the primary reviewer for continuing review and for review of changes in research.
- 4.8.1.3 Pharmacists and statisticians are assigned as reviewers for initial reviews. They do not generally serve as primary reviewers for

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other study submissions but may be asked to submit a review for any study under review in which their expertise is warranted.

4.8.2 Primary reviewers are recommended by the CIRB Operations Office and confirmed by the CIRB Chair with consideration being given to their qualifications in relation to the study.

4.8.3 If a CIRB member who has been assigned to serve as the primary reviewer for an agenda item finds that he/she will be unable to attend the meeting and present the review, the review will be reassigned.

4.8.4 In the event a CIRB member cannot attend the meeting as planned and the review cannot be reassigned, the assigned reviewer must post his/her review and it will be read and considered during deliberations.

4.8.5 If the CIRB member cannot attend the meeting as planned, the review cannot be reassigned and the review has not been posted, the Chair determines if a sufficient review can occur during the meeting. If not, the review will be rescheduled.

4.8.6 Reviews should be completed on ePanel[®] using the appropriate reviewer form with the form completed a minimum of two (2) days prior to the scheduled meeting.

4.9 Expedited Reviews

4.9.1 Expedited reviews are conducted by the Chair or Vice Chair. The Chair or Vice Chair may designate any CIRB member to perform expedited reviews with consideration being given to their experience and qualifications in relation to the study.

4.9.1.1 Reviewer experience is defined by the CIRB member’s role and the length of CIRB or prior IRB service.

4.9.2 Reviewers determine if a submission meets the regulatory criteria for expedited review and whether the submission satisfies the criteria for IRB approval as outlined in Federal regulations (45 CFR 46.111 and 21 CFR 56.111).

4.9.3 To expedite review of an amendment, reviewers determine that changes in research are minor changes that neither increase risk (45 CFR 46.110 and 21 CFR 56.110) nor materially change the risk/benefit ratio.

4.9.4 Reviewers have the responsibility of providing their review outcome to the CIRB Operations Office within 48 hours. If the reviewer cannot provide

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the review in the time period stipulated, such information is provided to the CIRB Operations Office at the time of assignment and the review will be reassigned.

4.9.5 Reviewers cannot overturn by expedited review an action taken by the convened CIRB, nor can they disapprove a submission.

4.10 Subject Matter Consultants Review

4.10.1 The CIRB Chair evaluates each research study placed on a pending agenda to ensure that the CIRB has the expertise and experience necessary to conduct an in-depth review of the protocol. Subject matter consultants may be used for the review of studies if determined necessary by the Chair. Consultants are not considered members of the CIRB and leave the discussion at the time of final deliberation and vote. Consultants will be asked to provide information to the CIRB members to allow for an informed decision about the risks and benefits of a study to be made. The services of an appropriate consultant will be coordinated by the Head, CIRB Initiative. NCI employees are excluded.

4.10.2 Consultants must sign a confidentiality agreement.

4.10.3 When a consultant is selected to provide any type of review, the consultant is asked to declare any conflicts of interest he/she has with respect to the proposed research. The criteria used for determining if a consultant has a conflict of interest are the same as for CIRB members. If the consultant declares a conflict or a potential conflict, the Conflict of Interest (COI) Subcommittee will determine whether the conflict would prevent the consultant from providing information to the CIRB. This decision must be based on the need for the consultant's expertise balanced against the potential for the conflict to influence the consultant such that the information provided by the consultant is biased. If the consultant has a conflict of interest, he/she may provide information as long as the conflict is disclosed to the CIRB. If the CIRB determines the conflict of interest prevents the consultant from providing information, another consultant will be identified.

4.11 Conflict of Interest Policy for CIRB Members

4.11.1 The purpose of this policy is to ensure that all deliberations of the CIRBs affecting participants in research projects are conducted by members whose overriding interest is the protection of those participants. At the same time, the policy is not intended to unnecessarily deny the CIRB the benefit of the expertise of any of its members in such deliberations.

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4.11.2 Conflicts of interest are assessed for all types of review conducted for each study. When it is determined that any member has an existing conflict of interest in a study before the CIRB, that member shall be absent throughout the deliberations concerning that study and voting, except when the Chair or a majority of the members not conflicted shall request that member’s presence for the purpose of responding to questions. If such a member has been requested to remain in the meeting to respond to questions, they will be absent for the final deliberation and vote. A member with a conflict of interest cannot be assigned as a reviewer.

4.11.3 Definition of a Conflict of Interest

4.11.3.1 A CIRB member has a conflict of interest when the member or her/his immediate family member (spouse, significant other or dependent child) or a person in a direct supervisory or reporting relationship with the member has a primary role in the oversight, design or conduct of the project or has a role in the analysis or management of the data. Management of the resulting conflict is commensurate with the level of involvement with the coordinating group or study. Specifically:

4.11.3.1.1 Serving on a governing body or other supervisory committee with group-wide oversight of the coordinating group that submitted the study may be managed by recusal from review of all studies submitted by that coordinating group. For example, a member who serves on the Board of Directors for a given coordinating group would be recused from review of all studies submitted by that group.

4.11.3.1.2 Serving on a Disease Committee, Working Group, or Data Monitoring Committee of the coordinating group that submitted the study for CIRB review may be managed by recusal from review of the specific study or group of studies within the scope of that committee. For example, a member who serves on the lung cancer committee of a coordinating group would be recused from review of all lung cancer studies from that group.

4.11.3.2 A member who serves as a Study Chair of a study under review with the CIRB has a conflict of interest for the CIRB’s review of that study.

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- 4.11.3.3 A CIRB member has a conflict of interest for the CIRB’s review of a study when the member is employed by the same institution as the Study Chair.
- 4.11.3.4 A CIRB member has a conflict of interest when the member or immediate family member has a financial interest of \$5,000 or more in any of the agents/devices/enterprises involved in the study under consideration, or in any direct competitor of such an enterprise. Ownership interests arising solely from investment in a company by a mutual, pension, or other institutional investment fund over which the CIRB member does not have control shall not be included as a conflict of interest.
- 4.11.3.5 A CIRB member has a conflict of interest when the member or immediate family member within two years before the deliberations receives any compensation from any enterprise involved in the study under consideration or from any direct competitor.
- 4.11.3.6 A CIRB member has a conflict of interest when the member or immediate family member has a proprietary interest in the research, such as a licensing agreement, copyright, patent, or trademark.
- 4.11.3.7 A CIRB member has a conflict of interest when the member is a Signatory Institution Principal Investigator for a study and has either:
 - 4.11.3.7.1 Identified a prospective participant for the study, or
 - 4.11.3.7.2 Enrolled a participant in the study or
 - 4.11.3.7.3 Performed or directed research interventions and interactions with the study participants. This restriction does not apply to other physicians who may be involved in the care of the patient, such as cross-over attendings, surgeons, or radiotherapists.
- 4.11.3.8 A CIRB member has a conflict of interest when the member could derive benefit (financial benefit, career advancement, or otherwise) based upon the outcome of the study.
- 4.11.3.9 A CIRB member has a conflict of interest when the member has an interest (financial or non-financial) that the CIRB or the CIRB member believes conflicts with or biases his/her ability to objectively review a study.

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4.11.3.10 Each CIRB member is responsible for disclosing conflicts of interest to the CIRB Operations Office as soon as possible. This disclosure should occur prior to the scheduled CIRB meeting, or at the beginning of the CIRB meeting, if not declared previously. If a CIRB member has questions regarding a potential conflict, the member must disclose the potential conflict to the CIRB Operations Office, who will forward the information to the appropriate CIRB Conflict of Interest Subcommittee for evaluation. If the Subcommittee does not have sufficient time to evaluate, the convened CIRB will make the determination.

4.11.3.11 A copy of this policy shall be posted as a reference document on ePanel[®] and the Chair shall call attention to the policy at the beginning of each meeting. An entry in each meeting’s minutes reflects adherence to this policy.

4.11.4 Conflict of Interest for CIRB Local Context Subcommittee Members

4.11.4.1 In addition to the conflicts identified above, the following is a conflict for members of the CIRB Local Context Subcommittee.

4.11.4.1.1 Employment or having a professional association with the Signatory Institution responsible for the conduct of the research or any Component or Affiliate Institutions.

4.12 Conflict of Interest Subcommittee

4.12.1 The purpose of the Conflict of Interest (COI) Subcommittee is to review potential conflicts of interest as disclosed by members when the member is not certain as to whether the disclosed relationship constitutes a conflict of interest requiring the member’s absence from the deliberations and vote.

4.12.2 The COI Subcommittee is composed of a subset of CIRB members who are appointed by the CIRB Chair. It is recommended that the three members be an ethicist, a scientific reviewer, and a patient advocate.

4.12.3 Members with uncertainty regarding potential conflicts must disclose the pertinent facts of the potential conflict in writing to the CIRB Operations Office. The disclosure must be submitted by the CIRB Operations Office

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to the CIRB Conflict of Interest Subcommittee for a determination prior to the CIRB meeting.

- 4.12.4 The COI Subcommittee reviews all such disclosures and renders a decision regarding whether the disclosure constitutes a conflict of interest. Members with conflicts under consideration by the COI Subcommittee are not to be named as primary reviewers.
 - 4.12.5 The COI Subcommittee presents a written report of its review no later than the beginning of such meeting where research in which the potential conflict exists will be reviewed.
 - 4.12.6 The CIRB must accept the determinations of the COI Subcommittee unless the determination was not unanimous.
 - 4.12.7 If a conflict or potential conflict affecting an item on the agenda for a convened meeting is disclosed too late for Subcommittee consideration, the issue shall be dealt with directly by the convened CIRB prior to discussion of the agenda item.
 - 4.12.8 If a potential conflict is disclosed by a member of the COI Subcommittee and sent to the Subcommittee for review, the CIRB Operations Office designates a CIRB member not conflicted to replace the disclosing COI Subcommittee member for the conflict determination.
- 4.13 CIRB Adverse Event Subcommittee
- 4.13.1 Studies approved by the CIRB have either a DSMB or the CIRB has determined the protocol includes a sufficient monitoring plan as required by 45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6). The CIRB may determine, based on the risks of the study, that CIRB review of individual adverse event reports is warranted for studies that do not have a DSMB or for which the CIRB has determined such review activity is required to ensure there is sufficient monitoring to satisfy the requirements of the regulations cited above. The CIRB will convene an Adverse Event Subcommittee to conduct review of individual adverse event reports in these cases.
 - 4.13.2 The CIRB Adverse Event Subcommittee consists of pediatric oncologists/medical oncologists, surgical oncologists, radiation oncologists, and pharmacists. Neither the Chair nor Vice Chair serves on the CIRB Adverse Event Subcommittee.
 - 4.13.3 Orientation of CIRB Adverse Event Subcommittee members starts after two months of continuous service.

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4.14 CIRB Local Context Subcommittee

4.14.1 Each CIRB maintains a Local Context Subcommittee to review the Annual Signatory Institution Worksheet, the Annual Principal Investigator Worksheet, the Study-Specific Worksheet, the Potential Unanticipated Problems and/or Serious or Continuing Noncompliance Reporting Worksheet, and any other documentation submitted by the Signatory Institution or Principal Investigator related to local context.

4.14.2 The CIRB Local Context Subcommittee consists of CIRB members with extensive experience with NCI-sponsored clinical research at the local institution level.

4.14.3 The CIRB Local Context Subcommittee members are designated expedited reviewers given the authority to approve local context considerations on behalf of the entire CIRB.

4.14.4 Orientation to the CIRB Local Context Subcommittee consists of training in the IT system used for review (IRBManager) and the process for review of submissions.

4.15 Independence of CIRB Members

4.15.1 The CIRB’s decision-making is independent of the NCI, coordinating groups, Study Chairs, and Signatory Institution Principal Investigators participating in NCI-sponsored studies. Individuals may be invited to participate in the CIRB meeting to provide the CIRB with the most up-to-date information for a specific study or situation on which to base its decision. These invited individuals are not otherwise involved in the CIRB’s decision-making and leave the CIRB meeting prior to final discussion and vote.

4.15.2 CIRB members will report to the CIRB Chair any attempts made by persons inside or outside of the CIRB to inappropriately influence that member’s decision to approve, require modifications to secure approval, or to disapprove any research activity or to suspend or terminate previously approved research.

4.15.3 If the Chair receives reports of attempts to unduly influence a CIRB member, he or she will discuss the issue with the Head, CIRB Initiative and a response plan will be developed. Responses could include:

4.15.3.1 Communication with the individual or group alleged to have attempted to influence the member; and

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4.15.3.2 Follow-up with CIRB member to determine if the attempts have ceased and to assess the affect the previous attempts might have had on the CIRB member’s independence in making determinations on that particular research.

4.15.4 The following efforts are made to protect the anonymity of the CIRB members:

4.15.4.1 CIRB members are not named in the version of the minutes and primary reviews posted on the website.

4.15.4.2 CIRB members have the option to remain anonymous in discussions with outside entities during conference calls.

4.15.4.3 Voting is anonymous.

4.15.4.4 Attendance at CIRB meetings is restricted to CIRB members, new CIRB members observing the CIRB meeting, CIRB Operations Office staff, NCI representatives, invited study representatives, subject matter consultants, and other individuals invited to provide the CIRB with information pertaining to its reviews.

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Section 5.0 Meeting Administration

5.1 Scheduling of Meetings

- 5.1.1 The Adult CIRB – Late Phase Emphasis and Adult CIRB - Early Phase Emphasis meet twice per month.
- 5.1.2 The Pediatric CIRB and Cancer Prevention and Control CIRB meet once per month.
- 5.1.3 Ad hoc meetings are held to discuss urgent matters affecting the protection of study participants.

5.2 Use of ePanel[®] for Convened Meetings

- 5.2.1 Regular CIRB meetings are conducted using an Internet-enhanced conference call via the ePanel[®] technology provided by Humanitas, Inc. Documents to be reviewed are posted on the ePanel[®] website. All CIRB members have access to ePanel[®] and receive training on how to access, participate in a meeting, and post reviews on ePanel[®]. Training of CIRB members and the CIRB Operations Office in the use of ePanel[®] is supplied by Humanitas, Inc.
- 5.2.2 If a CIRB member cannot access a computer, the member may still participate in the teleconference and vote verbally.
- 5.2.3 In extenuating circumstances, the CIRB may meet without using ePanel[®]. The CIRB Operations Office maintains a contingency plan to coordinate meetings without use of ePanel[®] which ensures all CIRB members have access to materials scheduled for review.

5.3 CIRB Operations Office Pre-Meeting Responsibilities

- 5.3.1 The CIRB Operations Office acknowledges the email notification from NCI when a study is submitted for initial review or when a study has changes in research. Study-specific documents for review are attached to NCI's email.
 - 5.3.1.1 No study is provided to the CIRB for initial review or review of changes in research without NCI's scientific review and approval.
 - 5.3.1.2 The CIRB may request a copy of the NCI's scientific review.

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- 5.3.2 The CIRB Operations Office acknowledges the email received from the Study Chair/coordinating group containing additional study-specific documents for CIRB review.
- 5.3.3 The CIRB Operations Office reviews all documents for completeness and collaborates with the Study Chair/coordinating group until the submission is complete. The CIRB reviews only final and complete versions of documents and does not review drafts or incomplete versions of documents.
- 5.3.4 When a submission is complete, the study is evaluated for expedited review. Studies that qualify are forwarded to the CIRB Chair, Vice Chair, or designee.
- 5.3.5 Studies that do not qualify for expedited review are assigned to an agenda for a convened CIRB meeting.
- 5.3.6 The Study Chair is informed via email of the meeting date when the convened CIRB will review the study.
- 5.3.7 The deadline for submission of study documents for CIRB review at the next convened meeting is two weeks before the scheduled meeting.

5.4 Assessment of CIRB Member COI for Study Reviews

To assess CIRB member conflicts of interest and to recommend primary reviewers for study submissions assigned to a CIRB meeting, the CIRB Operations Office forwards the following information to the CIRB members so that they may identify potential conflicts of interest with the studies on the agenda:

- 5.4.1 Type of review (initial review, continuing review, amendment review, etc.);
- 5.4.2 Study ID;
- 5.4.3 Study title;
- 5.4.4 Study Chair;
- 5.4.5 Study Chair’s institution/place of business;
- 5.4.6 Drug/agent involved in the study;
- 5.4.7 Drug/agent manufacturer; and

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5.4.8 Drug/agent supplier.

5.5 Generation of Meeting Agenda

5.5.1 Following the members’ disclosures of conflicts of interest and/or potential conflicts of interest with items scheduled for review, the CIRB Operations Office generates the meeting agenda.

5.5.2 The following are standard agenda items/sections:

- 5.5.2.1 Call to Order/Welcome;
 - 5.5.2.2 Reminder of COI policy and disclosure of conflicts;
 - 5.5.2.3 Monthly training presentation from the CIRB Operations Office.
 - 5.5.2.4 Review of minutes from a previous meeting (meeting date will be listed);
 - 5.5.2.5 Report from the CIRB Adverse Event Subcommittee, when applicable;
 - 5.5.2.6 General Business;
 - 5.5.2.7 Review of study submissions;
 - 5.5.2.8 List of Local Context Worksheets Approved by the CIRB Local Context Subcommittee;
 - 5.5.2.9 List of reviews and approvals conducted via CIRB expedited review procedures, including review of translated documents;
 - 5.5.2.10 List of other letters acknowledged by the CIRB Chair or CIRB Operations Office on behalf of the CIRB;
 - 5.5.2.11 Reminders and announcements for members, etc.; and
 - 5.5.2.12 Adjournment.
- 5.5.3 For each review item, the following information is listed on the agenda:
- 5.5.3.1 Time period assigned (e.g., 9:30 a.m. – 9:50 a.m.);
 - 5.5.3.2 Type of review;

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- 5.5.3.3 Primary reviewer(s);
- 5.5.3.4 Recused member(s);
- 5.5.3.5 Study ID Number;
- 5.5.3.6 Study title;
- 5.5.3.7 Protocol Version Date;
- 5.5.3.8 Expiration Date;
- 5.5.3.9 Study Chair;
- 5.5.3.10 Additional information may be included such as the applicable NCI Consent Form Template or prior Pediatric Risk Determinations.

5.6 Time Allocations for Review of Study Submissions

- 5.6.1 Each meeting is planned to last no longer than four (4) hours. If more items are received for review than time permits, the CIRB Operations Office consults with the CIRB Chair and NCI regarding review prioritization.
- 5.6.2 Items under time constraints and issues of participant safety or other human protections issues will be given priority and placed at the beginning of the agenda.
- 5.6.3 CIRB Operations Office provides a monthly training session for 15 minutes after the meeting is called to order.
- 5.6.4 The CIRB Operations Office assigns specific review times for each agenda item. The following guidelines are used for assigning review duration:
 - 5.6.4.1 Initial reviews are generally allotted a 60-minute review time.
 - 5.6.4.2 Amendment reviews are generally allotted a 15-minute review time.
 - 5.6.4.3 Continuing reviews are generally allotted a 10-minute review time.

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5.6.4.4 Study Chair response reviews are generally allotted a 10-minute review time.

5.6.4.5 Review of materials directed to study participants (for example, educational or recruitment material) are generally allotted a 10-minute review time.

5.6.4.6 Time zone of the Study Chair is considered and the agenda is developed to not contact a Study Chair on the West Coast prior to 11 a.m. Eastern Time, whenever possible.

5.6.5 If the CIRB is unable to review an agenda item due to time constraints or quorum issues during the convened meeting, the agenda item will be rescheduled.

5.7 Notification of External Participants

Attendance at CIRB meetings is limited to CIRB members, new CIRB members observing the CIRB meeting, CIRB Operations Office staff, NCI representatives, invited study representatives, subject matter consultants, and other individuals invited to provide the CIRB with information pertaining to its reviews.

5.7.1 The CIRB Operations Office notifies the following external participants, as appropriate, of the meeting date and assigned review time: the Study Chair, coordinating group representative, the CTEP disease therapeutic head, the Biostatistics Research Branch (BRB) statistician, DCP Representatives when applicable, and others as appropriate.

5.7.2 External participants are invited to every initial review and may be invited to contribute to any other CIRB review pertaining to their study.

5.7.3 The role of external participants is to:

5.7.3.1 Respond to questions from the CIRB Chair or members that pertain to: study background or any other section of the protocol; provide clarification of study activities or related documents; proactively consider, or even address, any concerns the CIRB might have that may result in a stipulation; answer any other question the CIRB might have.

5.7.3.2 Provide a suitable back-up if they are unable to attend the meeting. If an invitee or designee does not attend, the CIRB will move forward with the review.

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5.7.4 The Chair, and other CIRB members, may speak with any external participant prior to the meeting to gather more information regarding concerns raised by reviewers. This activity is coordinated by the CIRB Operations Office and the discussion includes at least one member of the CIRB Operations Office.

5.7.5 If during the CIRB meeting, the CIRB identifies questions or changes that require resolution before final approval can be granted, the CIRB will contact the external participants to address these issues and to ensure the CIRB has the most current information upon which to base its decision. If the CIRB is unable to reach the external participants during the meeting, the CIRB may move forward with its review.

5.8 Distribution of Materials for Review

5.8.1 Documents scheduled for review are available to the CIRB members one weekend prior to the scheduled meeting. Additional supporting documents or updated submission documents may be provided as soon as they are available. The following documents will be made available, as appropriate:

5.8.1.1 Completed applications;

5.8.1.2 Summary of changes for amendments and Study Chair responses;

5.8.1.3 Protocols;

5.8.1.4 Model consent forms/Parental permission forms;

5.8.1.5 Other documents requiring review including but not limited to forms, questionnaires, recruitment materials, etc. directed to current or potential study participants;

5.8.1.6 Primary reviewers and pharmacists receive a copy of the Investigator’s Brochure when the research involves an agent that has not been approved by the FDA;

5.8.1.7 Recent literature, DSMB reports, summary of study activity, interim findings, and other reports pertinent to the continued approval of the research;

5.8.1.8 Reports of complaints, audits, unexpected events, and any other material submitted for review that does not meet the requirements for expedited review;

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5.8.1.9 Reports from the CIRB Adverse Event Subcommittee, when applicable.

5.8.2 Materials related to any expedited review are available to CIRB members upon request.

5.8.3 Members with disclosed conflicts of interest have access to all meeting materials but are recused from the final discussion and the vote on the items for which they have disclosed a conflict. Members who are recused due to conflict of interest do not count toward quorum for the review and do not vote for items for which they are conflicted.

5.9 Administrative Considerations Based on Review Type

5.9.1 Initial Review

5.9.1.1 An initial review submission consists of the following documents:

- 5.9.1.1.1 Study protocol;
- 5.9.1.1.2 Model consent form/Parental permission form;
- 5.9.1.1.3 Youth Information Sheets, when applicable;
- 5.9.1.1.4 Approval from NCI;
- 5.9.1.1.5 NCI CIRB Application for Treatment Studies or the CIRB Ancillary Protocol Review Application;
- 5.9.1.1.6 Investigator Brochure, if applicable;
- 5.9.1.1.7 Study instruments to be completed by the participant, if applicable; and
- 5.9.1.1.8 Recruitment material, if applicable.

5.9.1.2 The CIRBs are constituted to provide appropriate expertise for studies involving their respective populations. Studies enrolling adolescents and young adults have the potential of crossing the age threshold of the reviewing CIRB, thus requiring the participation of subject matter consultants to ensure the appropriate expertise is available to provide a complete study review. Subject matter consultants are selected per CIRB policy pertaining to Subject Matter Consultants Review.

- 5.9.1.2.1 The Pediatric CIRB secures subject matter consultants for pediatric studies that intend to enroll young adults, when needed.
- 5.9.1.2.2 The Adult CIRBs and CPC CIRB secure subject matter consultants for adult studies that intend to enroll adolescents.

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5.9.1.3 For each initial review for which the CIRB requires modifications or additional information, the CIRB contacts the Study Chair and representatives from the coordinating group and CTEP or DCP Representatives during the CIRB’s meeting as described in section 5.6.5.

5.9.1.4 The study expiration date is established at the time of initial review of a study and at subsequent continuing reviews of the study. The expiration date is the date of CIRB approval of the study submission plus the approval interval minus one day. For example, if the approval interval is one year, the expiration date is one year minus one day from the date of CIRB approval.

5.9.2 Study Chair Response

5.9.2.1 A Study Chair response submission consists of the following documents:

- 5.9.2.1.1 Study Chair’s written response to the CIRB’s stipulations;
- 5.9.2.1.2 Revised study protocol, when applicable;
- 5.9.2.1.3 Revised Model consent form/Parental permission form, when applicable;
- 5.9.2.1.4 Revised Youth Information Sheets, when applicable;
- 5.9.2.1.5 Revised NCI CIRB Application for Treatment Studies or the CIRB Ancillary Protocol Review Application;
- 5.9.2.1.6 Summary of CIRB Application Revisions, when applicable; and
- 5.9.2.1.7 Any other documents previously reviewed by the CIRB that have been modified per the CIRB’s requests.

5.9.2.2 It is preferred that Study Chair responses include only changes requested by the CIRB. When additional changes are made, the revised documents are forwarded to NCI for approval prior to CIRB review.

5.9.2.3 If the study was approved pending modification by the CIRB and all requested changes have been made, the study may be reviewed by expedited review procedures. The Chair may determine that any response requires convened CIRB review.

5.9.2.4 If the study was tabled by the CIRB, review by the convened CIRB is required.

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5.9.3 Amendments (Changes in Research)

5.9.3.1 An amendment review submission consists of the following documents:

- 5.9.3.1.1 Summary of Changes;
- 5.9.3.1.2 Study protocol;
- 5.9.3.1.3 Model consent form/Parental permission form;
- 5.9.3.1.4 Revised Youth Information Sheets, when applicable
- 5.9.3.1.5 Approval from NCI;
- 5.9.3.1.6 CIRB Amendment Review Application; and
- 5.9.3.1.7 Any other documents previously reviewed by the CIRB that have been modified as part of the amendment.

5.9.3.2 When an amendment is submitted to the CIRB in response to requests by the CIRB, the CIRB Operations Office reviews it to ensure that the requested changes were made.

5.9.3.3 If the Study Chair has made substantive (more than administrative) revisions in addition to the CIRB requests, the CIRB Operations Office sends the amendment to NCI and no further action will be taken by CIRB until NCI has approved the non-CIRB requested changes.

5.9.3.4 A CIRB Amendment Review Application specific to the amendment’s Protocol Version Date is required and is submitted directly to the CIRB by the Study Chair.

5.9.3.5 Amendments to studies previously approved by the CIRB that enroll adolescents and young adults may require subject matter consultants to ensure the appropriate expertise is available to provide a complete review of the amendment. Whenever possible the same subject matter consultant should be used throughout the life-cycle of a study. Subject matter consultants are selected per CIRB policy pertaining to Subject Matter Consultants Review.

- 5.9.3.5.1 For pediatric studies that intend to enroll young adults, the CIRB Chair may request the written review of a subject matter consultant prior to the meeting however the consultant need not attend the CIRB meeting. The Chair may also request the attendance of the subject matter consultant.

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5.9.3.5.2 For adult studies that intend to enroll adolescents, the CIRB Chair will request the written review of a subject matter consultant prior to the meeting. The consultant is encouraged to attend the meeting to address pediatric risk determinations.

5.9.4 Memos from Coordinating Group to Investigators and/or Research Staff

5.9.4.1 A coordinating group memo submission for review consists of the memorandum from the coordinating group and any other documents distributed by the coordinating group associated with the memorandum.

5.9.4.2 Coordinating group memos which may impact the conduct of the research are submitted by the Study Chair to the CIRB and are forwarded to the CIRB Chair for determination of the need for review.

5.9.4.3 If the coordinating group memo makes a change to the protocol or consent form, the memo will not be accepted by the CIRB. An amendment implementing the change must be submitted to the Protocol Information Office (PIO) to be processed as described in sections 5.9.3 or 5.9.5.

5.9.5 Editorial or Administrative Amendment

5.9.5.1 An editorial or administrative amendment submission consists of the following documents:

- 5.9.5.1.1 Summary of Changes;
- 5.9.5.1.2 Updated study protocol;
- 5.9.5.1.3 Model consent form/Parental permission form;
- 5.9.5.1.4 Approval on Hold from NCI.

5.9.5.2 The Study Chair is required to submit editorial or administrative amendments to the PIO. The CIRB receives editorial or administrative amendments with an Approval on Hold from PIO.

5.9.5.3 The CIRB Operations Office reviews editorial or administrative amendments according to section 8.5 of these SOPs.

5.9.6 Continuing Review

5.9.6.1 A continuing review submission consists of the following documents provided by the Study Chair:

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- 5.9.6.1.1 NCI CIRB Application for Continuing Review which includes, the number of participants accrued, number of participants who have withdrawn and the reason for withdrawal; summary of reports of unanticipated problems involving risks to participants or others or any serious or continuing noncompliance; complaints about the research; amendments or modifications; relevant recent literature; and interim findings;
 - 5.9.6.1.2 Data Safety Committee reports or equivalent, as applicable;
 - 5.9.6.1.3 Study protocol;
 - 5.9.6.1.4 Model consent form/Parental permission form;
 - 5.9.6.1.5 Youth Information Sheets, when applicable; and
 - 5.9.6.1.6 Updated Investigator’s Brochure, if applicable.
- 5.9.6.2 Approximately three months prior to the expiration of the current study approval, the CIRB Operations Office notifies the Study Chair of the date of last review, expiration date of CIRB approval, the Protocol Version Date upon which to base the application, and the submission deadline date for documents to be returned to the CIRB. A copy of the current CIRB Application for Continuing Review accompanies the notification.
- 5.9.6.3 The Study Chair must complete the CIRB Application for Continuing Review and return it with the required supporting documents to the CIRB Operations Office no later than the submission deadline designated on the continuing review notice.
- 5.9.6.4 CIRB continuing review is based on the currently approved or approved pending modification version of the protocol and model consent form.
- 5.9.6.4.1 If an amendment is approved or approved pending modifications after the submission of the CIRB Continuing Review Application, but prior to review for continuation by the CIRB, the CIRB Operations Office updates the CIRB Application for Continuing Review to reflect the version date of the recently approved or approved pending modifications amendment. A copy of the updated CIRB Application for Continuing Review will be provided to the Study Chair.

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5.9.6.5 If the NCI CIRB Application for Continuing Review is not received by the designated deadline, the CIRB Operations Office will inform the Study Chair of the urgent need for the submission.

5.9.6.6 If the Study Chair does not provide continuing review information to the CIRB, or if the CIRB has not approved the study by the expiration date for any other reason, no new subjects may be enrolled and all research activities must stop unless the CIRB determines that it is in the best interest of the individual participants to continue participating.

5.9.6.7 The study expiration date is established at the time of initial review of a study and at subsequent continuing reviews of the study. The expiration date is the date of CIRB final approval of the study submission plus the approval interval minus one day. For example, if the approval interval is one year, the expiration date is one year minus one day from the date of CIRB approval.

5.9.6.8 For continuing review of studies previously approved by the CIRB that enroll adolescents and young adults, the CIRB Chair may request the review of subject matter consultants to ensure the appropriate expertise to address the unique circumstances of the population. Whenever possible the same subject matter consultant should be used throughout the life-cycle of a study. Subject matter consultants are selected per CIRB policy pertaining to Subject Matter Consultants Review.

5.9.6.8.1 For pediatric studies that are enrolling young adults, the CIRB Chair may request the written review of a subject matter consultant prior to the meeting in lieu of the subject matter consultant attending the meeting. The Chair may also request the attendance of the subject matter consultant.

5.9.6.8.2 For adult studies that intend to enroll adolescents, the CIRB Chair may request the written review of a subject matter consultant prior to the meeting. The consultant is encouraged to attend the meeting to address pediatric risk determinations.

5.9.7 Recruitment Material

5.9.7.1 A recruitment material submission consists of the following:

5.9.7.1.1 A copy of the recruitment material;

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- 5.9.7.1.2 CIRB Amendment Review Application; and
- 5.9.7.1.3 A plan for the distribution of the recruitment materials.

5.9.8 Materials Directed to Study Participants

5.9.8.1 A submission for materials for study participants consists of the following:

- 5.9.8.1.1 A copy of the material to be provided to the study participant; and
- 5.9.8.1.2 CIRB Amendment Review Application; and
- 5.9.8.1.3 Any other documents requiring updating based on the new material provided. These could include an updated protocol, model consent form, or plan for distribution.

5.9.9 Translated Documents

Translated copies of CIRB-approved documents such as consent forms or recruitment materials, may be submitted by the Study Chair or Principal Investigator to the CIRB. On behalf of the CIRB, CIRB Operations Office staff complete the verification process described below (and in section 8.9), and issue approval on behalf of the CIRB.

5.9.9.1 A complete submission for review of translated documents includes:

- 5.9.9.1.1 A completed application for review of translated documents including:
 - a. The study ID number and title,
 - b. Current Protocol Version Date, and
 - c. The name of the document to be reviewed.
- 5.9.9.1.2 A copy of the CIRB-approved English language document corresponding to the current Protocol Version Date,
- 5.9.9.1.3 A translated copy of the CIRB-approved English language document corresponding to the current Protocol Version Date,
- 5.9.9.1.4 A Certificate of Accuracy from the translator or equivalent document,
- 5.9.9.1.5 A copy of the CIRB-approved protocol with corresponding Protocol Version Date, and

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- 5.9.9.1.6 A copy of the CIRB approval letter for the English language document and protocol with corresponding Protocol Version Date.

- 5.9.9.2 The CIRB Operations Office reviews the submission for completeness and confirms the following:
 - 5.9.9.2.1 The corresponding English language document and protocol are CIRB-approved, and
 - 5.9.9.2.2 The version of all submitted corresponds to the most current CIRB-approved protocol. For documents that do not include a Protocol Version Date, such as recruitment brochures, the translated document must match the version number or other version date of the corresponding CIRB-approved English language document.
 - 5.9.9.2.3 On occasion, the most current CIRB-approved versions of the documents may be a more recent version than those which have been distributed by the Study Chair to participating sites. In these cases, the CIRB Operations Office will consider the version available to participating sites to be the most current CIRB-approved versions for purposes of verification of translated documents.

- 5.9.9.3 The CIRB Operations Office obtains available translations from the Cancer Trials Support Unit for review by the CIRB.
 - 5.9.9.3.1 The CIRB Operations Office completes the submission for review on behalf of the Study Chair, completes the verification on behalf of the CIRB, and notifies the Study Chair upon approval.

- 5.9.9.4 If an amendment to the study results in no changes to previously translated documents except for the Protocol Version Date, the existing CIRB-approved translated document may continue to be used.
 - 5.9.9.4.1 The CIRB Operations Office verifies there have been no changes to the CIRB-approved English language version of the translated documents as a result of the amendment and updates the protocol version date on the translated document, if applicable. This verification and review may be completed by the

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CIRB as part of its review of an amendment or after CIRB-approval of amendment.

5.9.9.5 For validated instruments that are available in languages other than English, the CIRB’s approval of the English instrument as part of its review of a study is considered to extend to the validated translated versions. In general, the protocol should indicate the languages in which the instrument is available and provide investigators with information on how to obtain the translated instrument.

5.9.10 Request for Rapid Amendments (RRA)

5.9.10.1 An RRA submission consists of the following:

- 5.9.10.1.1 A copy of the RRA;
- 5.9.10.1.2 A copy of the action letter and/or the CAEPR; and
- 5.9.10.1.3 A listing of the studies affected.

5.9.10.2 The CIRB Operations Office reviews the RRA submission to determine if any CIRB studies are affected.

5.9.10.2.1 For those studies affected, the information is acknowledged and the CIRB Operations Office does not take any further action until the official amendment submission is received.

5.9.10.3 The CIRB Operations Office processes the official amendment as it would any other amendment submission with a greater emphasis on timing of the review.

Upon receipt of the official amendment the RRA is forwarded to the CIRB Chair to determine if the amendment qualifies for expedited review as outlined in the OHRP Correspondence dated September 29, 2008 and located at the following URL:

<https://www.hhs.gov/ohrp/regulations-and-policy/guidance/september-29-2008-letter-to-jeffrey-abrams/index.html>.

5.9.10.3.1 If the changes do not qualify for expedited review, the CIRB Chair notifies CTEP and accrual to the study must be suspended until the consent form can be revised.

5.9.10.3.2 If the changes qualify for expedited review, the CIRB Chair may approve the amendment.

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5.9.11 Adverse Event Review

5.9.11.1 The CIRB does not review individual adverse event reports pertaining to treatment studies when the study has a DSMB or the CIRB has determined the monitoring plan is sufficient. The CIRB reviews DSMB reports and study toxicity reports submitted at the time of continuing review.

5.9.11.2 An adverse event review submission distributed to the CIRB Adverse Event Subcommittee member consists of the following documents:

5.9.11.2.1 Adverse event reports as submitted to the CIRB Operations Office;

5.9.11.2.2 Current consent form; and

5.9.11.2.3 SAE Reviewer Worksheet.

5.9.11.3 The report from the CIRB Adverse Event Subcommittee compiled by the CIRB Operations Office is generated prior to each convened CIRB meeting. This report lists the adverse events for which the CIRB Adverse Event Subcommittee has rendered a recommendation to the CIRB. During the convened meeting, the CIRB Adverse Event Subcommittee members provide comments on and make recommendations to the CIRB based on their review of the adverse events documented in the report from the CIRB Adverse Event Subcommittee.

5.9.11.4 Any determination by a Subcommittee member or the convened CIRB that indicates a need to clarify an existing risk or to add a new risk to the consent form requires contacting the IND holder to gather more information as to why the change was not previously made. If the IND is not held by CTEP, the Cooperative Group, or there is no IND, the request for more information will be forwarded to the Cooperative Group.

5.9.12 Local Context Review

5.9.12.1 Annual Signatory Institution Worksheet

5.9.12.1.1 The submission of the Annual Signatory Institution Worksheet consists of the completed Worksheet which includes any boilerplate language and other institutional requirements required by the Signatory

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Institution for inclusion in the consent form for NCI studies.

- 5.9.12.1.2 The CIRB Operations Office conducts an administrative review of the Annual Signatory Institution Worksheet to confirm completeness.
- 5.9.12.1.3 The CIRB Operations Office forwards the submission, including the administrative review, to the CIRB Local Context Subcommittee member for a final determination.

5.9.12.2 Annual Principal Investigator Worksheet

- 5.9.12.2.1 The submission of the Annual Principal Investigator Worksheet consists of the completed Worksheet which includes information regarding the informed consent process for the Principal Investigator’s research staff and vulnerable populations that could be enrolled by the Principal Investigator into NCI research.
- 5.9.12.2.2 The CIRB Operations Office conducts an administrative review of the Annual Principal Investigator Worksheet to confirm completeness.
- 5.9.12.2.3 The CIRB Operations Office forwards the submission, including the administrative review, to the CIRB Local Context Subcommittee member for a final determination.

5.9.12.3 Study-Specific Worksheet

- 5.9.12.3.1 A Principal Investigator with an approved Annual Principal Investigator Worksheet submits a Study-Specific Worksheet to open a study.
- 5.9.12.3.2 The Study-Specific Worksheet confirms the Principal Investigator will conduct the study according to their approved Annual Principal Investigator Worksheet with no changes. If the Principal Investigator’s conduct of a study requires changes from the information provided in the Annual Principal Investigator Worksheet, these changes are captured in the Study-Specific Worksheet.
- 5.9.12.3.3 The CIRB Operations Office conducts an administrative review to confirm completeness.
- 5.9.12.3.4 If a study requires changes from the information provided in the Annual Principal Investigator Worksheet, the CIRB Operations Office forwards the

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submission and the administrative review to the CIRB Local Context Subcommittee member for a final determination as described in section 8.13 of this SOP.

5.9.12.3.5 If the Principal Investigator confirms in the Study-Specific Worksheet that the Principal Investigator will conduct the study according to their approved Annual Principal Investigator Worksheet, the CIRB Operations Office issues approval on behalf of the CIRB as described in section 8.13 of this SOP.

5.9.12.3.6 The Annual Signatory Institution Worksheet and the Annual Principal Investigator Worksheet are readily accessible by CIRB Local Context Subcommittee Members and CIRB Operations Office to use as an additional resource.

5.9.12.4 Potential Unanticipated Problem and/or Serious or Continuing Noncompliance Reporting Form

5.9.12.4.1 The submission consists of the Potential Unanticipated Problem and/or Serious or Continuing Noncompliance Reporting Worksheet and a management plan for the incident, experience, or outcome.

5.9.12.4.2 The CIRB Operations Office conducts an administrative review of the Reporting Form and management plan to confirm completeness.

5.9.12.4.3 The CIRB Operations Office forwards the submission, including the administrative review, to the CIRB Local Context Subcommittee member for a determination.

5.9.12.5 Locally-Developed Material

5.9.12.5.1 The locally-developed material directed to study participants or translations of CIRB-approved documents is submitted via the Annual Signatory Institution Worksheet or the Study-Specific Worksheet. The submission consists of the Worksheet and supporting documents for review.

5.9.12.5.2 The CIRB Operations Office conducts an administrative review of the Worksheet and supporting documents to confirm completeness.

5.9.12.5.3 The CIRB Operations Office forwards the submission, including the administrative review, to

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the CIRB Local Context Subcommittee member for a final determination. Verification of translated documents may be completed by CIRB Operations Office staff per section 5.9.9 of these SOPs.

5.9.12.6 Study Closure or Transfer of Study IRB Review Responsibility Form

5.9.12.6.1 Signatory Institution Principal Investigators may close a study at their institution when all of the following are true:

- a. The study is closed to accrual at the Signatory Institution and all Component and/or Affiliate Institutions relying on the Signatory Institution for this study.
- b. All study participants on this study have completed study intervention(s) and follow-up activities OR no study participants were enrolled.
- c. There will be no further research activities for this study (this includes recruitment, enrollment, data collection, data analysis, data submission, etc.).

5.9.13 Study Completion with the CIRB

5.9.13.1 A study is only completed with the CIRB when it has finished its planned course and all the following are true:

- 5.9.13.1.1 The study has been permanently closed to accrual;
- 5.9.13.1.2 All study participants have completed study intervention and interactions.
- 5.9.13.1.3 All study-related collection of identifiable private information about the subjects is complete.
- 5.9.13.1.4 Analysis of identifiable data is complete; and
- 5.9.13.1.5 The study has met its primary objectives and a final study report/publication has been submitted

5.9.13.2 A study may be considered administratively complete with the CIRB if the study was stopped earlier than planned and items 5.9.13.1.1, 5.9.13.1.2 and 5.9.13.1.3 above are true and no further study activity or data analysis will be performed.

5.9.13.3 To close a study with the CIRB, the Study Chair submits a completed CIRB Application for Continuing Review indicating the study status as “completed” or “administratively completed.”

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5.9.13.4 CIRB Operations Office staff review the submitted application and forward the request for study completion to the CIRB Administrator for acknowledgment on behalf of the CIRB.

5.9.13.5 When a study is completed with the CIRB, all institutions participating in the site are considered complete for that study.

5.10 Primary Reviewer Assignments

5.10.1 CIRB Reviewer Assignments

5.10.1.1 At least one primary reviewer is assigned to each agenda item. Members will be chosen as primary reviewers on a rotating basis to ensure that responsibilities are evenly distributed with priority given to CIRB members who have previously reviewed the study to ensure continuity.

5.10.1.2 The pharmacist and the statistician are not assigned as primary reviewers because they have the responsibility to review all submissions pertaining to their discipline.

5.10.2 The CIRB Operations Office recommends primary reviewer assignments to the CIRB Chair or Vice Chair based on CIRB member responses to the pre-meeting COI query.

5.10.3 Reviewer assignments are communicated to all members via email at least one weekend prior to the scheduled meeting and noted on the specific meeting agenda.

5.11 Management of Recused Members

5.11.1 CIRB members who are recused from review of a study leave the meeting and do not participate in the final deliberations and vote. CIRB members who are recused do not count toward quorum.

5.11.2 The CIRB Operations Office ensures recused CIRB members rejoin the meeting when review of the study for which they are conflicted is complete.

5.12 Quorum

5.12.1 A quorum is required to conduct a CIRB meeting. A quorum is defined as a majority of the members of the CIRB and includes at least one non-scientific member (lay person) and one scientific member.

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5.12.2 The CIRB Operations Office documents each CIRB member’s attendance, including arrivals, departures, and recusals, and assures that a quorum is maintained at all times during the meeting.

5.12.3 If a CIRB member and their alternate are both in attendance, the alternate does not count toward quorum. Alternates count toward quorum only when the primary member for whom they are an alternate is not in attendance.

5.12.4 If quorum is lost during a meeting, the CIRB Operations Office will immediately notify the Chair and the CIRB meeting will adjourn unless quorum can be re-established.

5.12.5 Recused members do not count towards quorum.

5.13 Voting

5.13.1 For a motion or recommendation to be approved, a majority of members present must vote in the affirmative.

5.13.2 Members may vote:

5.13.2.1 “Yes” signifying their agreement with a motion or recommendation.

5.13.2.2 “No” signifying their disagreement with a motion or recommendation.

5.13.2.3 “Abstain” if the member was absent for the discussion of an item under review.

5.13.3 All members in attendance count toward quorum. If a CIRB member and their alternate are both in attendance, the alternate does not vote and does not count toward quorum. Alternates vote and count toward quorum only when the primary member for whom they are an alternate is not in attendance.

5.13.4 If quorum is lost, the CIRB cannot vote on any agenda item until quorum is restored.

5.13.5 Votes are not permitted by proxy.

5.14 Review Outcome Letters

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- 5.14.1 A review outcome letter to the Study Chair is required to be sent whenever the CIRB votes on a review.
- 5.14.2 Review outcome letters are addressed to the Study Chair with appropriate individuals copied.
- 5.14.3 Distribution of review outcome letters takes place within seven (7) to ten (10) business days of the convened meeting.
- 5.14.4 Review outcome letters are posted on the study-specific web pages of the CTSU website under the CIRB Documents tab for coordinating groups utilizing the CTSU website to distribute documents.
- 5.14.5 Review outcome letters include the Protocol Version Date for the protocol and consent form(s) reviewed and the following additional information, as applicable:
 - 5.14.5.1 Statement of CIRB action;
 - 5.14.5.2 Date of CIRB review;
 - 5.14.5.3 List of documents reviewed (protocol, consent form, Investigator Brochure, advertisements, etc.);
 - 5.14.5.4 Statement of any determinations made related to the populations included in the research; and
 - 5.14.5.5 Protocol deviation compliance issues and reporting expectations.
- 5.14.6 A copy of the CIRB–approved consent form(s) is attached to the review outcome letter, when applicable.
- 5.14.7 CTEP or DCP receives a copy of approval notifications for initial and amendment reviews.
- 5.14.8 In addition to the information included in all review outcome letters, initial approval notifications include the following:
 - 5.14.8.1 CIRB approval date;
 - 5.14.8.2 Expiration date of CIRB approval;
 - 5.14.8.3 Statement regarding the number of participants approved for enrollment; and

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- 5.14.8.4 Statement that approval does not include the enrollment of prisoners.

- 5.14.9 In addition to the information required for all review outcome letters, approval pending modification and tabling notifications include the following:
 - 5.14.9.1 Stipulations required by the CIRB to secure approval;
 - 5.14.9.2 The basis for requiring the stipulations or for tabling;
 - 5.14.9.3 The request for a response within an appropriate time frame;
 - 5.14.9.3.1 If the approval pending modification is for an initial review, a response is requested within 14 days of receipt of the notification.
 - 5.14.9.3.2 If the approval pending modification is for a continuing review, a response is requested within seven (7) to ten (10) days of receipt of the notification.
 - 5.14.9.4 A statement that the Study Chair may conference call with the CIRB Chair by sending an email to the CIRB Operations Office if he or she has questions regarding the stipulations; and
 - 5.14.9.5 If this is the second time this item has been reviewed by the CIRB, then there should be a statement informing the Study Chair that a conference call with the CIRB Chair to discuss the CIRB’s actions will be arranged.

- 5.14.10 In addition to the information required for all review outcome letters, disapproval notifications include the following:
 - 5.14.10.1 The basis for disapproval;
 - 5.14.10.2 A statement that the Study Chair may conference call with the CIRB Chair by sending an email to the CIRB Operations Office if he or she has questions regarding the CIRB’s action;
 - 5.14.10.3 A statement that if the Study Chair is still interested in pursuing the research question, the protocol must be rewritten and submitted as a new study; and
 - 5.14.10.4 If this is the second time this item has been reviewed by the CIRB, then there should be a statement informing the Study

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Chair that a conference call with the CIRB Chair to discuss the CIRB’s actions will be arranged.

5.14.11 In addition to the information required for all review outcome letters, letters based on conversation with the Study Chair and CTEP or DCP, to suspend enrollment, suspend other research activity, withdraw or terminate approval of research include the following:

- 5.14.11.1 The basis for the action;
- 5.14.11.2 If applicable, stipulations required by the CIRB to lift suspension or secure approval;
- 5.14.11.3 If applicable, the request for a response within an appropriate time frame; and
- 5.14.11.4 A statement that the Study Chair may conference call with the CIRB Chair by sending an email to the CIRB Operations Office if he or she has questions regarding the CIRB’s actions.

5.14.12 Review outcome letters related to local context consideration review include the following information:

- 5.14.12.1 Type of Worksheet reviewed;
- 5.14.12.2 Statement of the CIRB action which can only be approved or approved pending modification;
- 5.14.12.3 CIRB review date;
- 5.14.12.4 Signatory Institution, Principal Investigator, or Study reviewed;
- 5.14.12.5 Component and Affiliate Institutions included in the review of the Annual Signatory Institution Worksheet, when applicable;
- 5.14.12.6 Listing of all required boilerplate language and other institutional requirements to be included in the consent form in the outcome letter for the Annual Signatory Institution Worksheet;
- 5.14.12.7 Statement regarding the responsibilities of the Signatory Institution or Principal Investigator.

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5.15 Meeting Minutes

5.15.1 Minutes for each meeting are written to include the following:

- 5.15.1.1 Date of meeting and time meeting started;
- 5.15.1.2 Names of meeting attendees;
- 5.15.1.3 CIRB member’s attendance, absences, departures, and returns;
- 5.15.1.4 Presence of quorum;
- 5.15.1.5 Actions taken by the CIRB, and the vote on these actions including the number of members voting for, against, and abstaining;
- 5.15.1.6 Names of the members who leave the meeting for conflicts of interest;
- 5.15.1.7 For each agenda item, the following are documented:
 - 5.15.1.7.1 The basis for requiring changes in or disapproving research;
 - 5.15.1.7.2 Determinations regarding inclusion of vulnerable subjects, including those with diminished capacity;
 - 5.15.1.7.3 Summary of the discussion, including consultant input, controverted issues and their resolution, and any discussion with external participants;
 - 5.15.1.7.4 Dissenting reports and opinions;
 - 5.15.1.7.5 Determinations required by the regulations and study specific findings justifying those determinations for:
 - a. Waiver or alteration of the consent process;
 - b. Research involving pregnant women, fetuses and neonates;
 - c. Research involving children;
 - d. Risk determination (for initial reviews only);
 - e. The rationale for significant risk/non-significant risk device determinations.
- 5.15.1.8 For initial and continuing review, the length of the approval period;
- 5.15.1.9 Documentation for the rationale for conducting continuing review of research that would otherwise not require continuing

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review (per 45 CFR 46.109(f) (applicable under 2018 Requirements only));

and

5.15.1.10 Time of adjournment.

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Section 6.0 Expedited Review

6.1 Federally-Defined Categories for Expedited Review

6.1.1 Initial review may occur through expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110 if the research (1) presents no more than minimal risk to human subjects, and (2) involves only procedures listed in one or more of the following categories and the reviewer determines that the study is minimal risk. For research approved after January 21, 2019, the following additional category may be used for expedited review of initial reviews (3) research for which limited IRB review is a condition of exemption. The categories eligible for expedited review for continuing review as found in the Federal Register are located at the following URL: <http://www.hhs.gov/ohrp/policy/expedited98.html>.

Studies initially reviewed under these categories may undergo continuing review under these same categories.

6.1.1.1 Clinical studies of drugs and medical devices only when the following conditions are met:

6.1.1.1.1 Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.); and

6.1.1.1.2 Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

6.1.1.2 Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

6.1.1.2.1 From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or

6.1.1.2.2 From other adults and children², considering the age, weight, and health of the subjects, the collection

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procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

- 6.1.1.3 Prospective collection of biological specimens for research purposes by noninvasive means such as:
 - 6.1.1.3.1 Hair and nail clippings in a non-disfiguring manner;
 - 6.1.1.3.2 Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
 - 6.1.1.3.3 Permanent teeth if routine patient care indicates a need for extraction;
 - 6.1.1.3.4 Excreta and external secretions (including sweat);
 - 6.1.1.3.5 Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
 - 6.1.1.3.6 Placenta removed at delivery;
 - 6.1.1.3.7 Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
 - 6.1.1.3.8 Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
 - 6.1.1.3.9 Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
 - 6.1.1.3.10 Sputum collected after saline mist nebulization.

- 6.1.1.4 Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications). Examples include:
 - 6.1.1.4.1 Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

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- 6.1.1.4.2 Weighing or testing sensory acuity;
- 6.1.1.4.3 Magnetic resonance imaging;
- 6.1.1.4.4 Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
- 6.1.1.4.5 Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

6.1.1.5 Non-exempt research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

6.1.1.6 Collection of data from voice, video, digital, or image recordings made for research purposes.

6.1.1.7 Non-exempt research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identify, language, communication, cultural beliefs of practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

6.1.2 Continuing review of studies initially reviewed by the convened CIRB may be completed through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110 if the research (1) presents no more than minimal risk to human subjects, and (2) involves only procedures listed in one or more of the following categories. The categories eligible for expedited review for continuing review as found in the Federal Register are located at the following URL:
<http://www.hhs.gov/ohrp/policy/expedited98.html>.

6.1.2.1 Category 8: Continuing review of research previously approved by the convened IRB as follows:

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

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- 6.1.2.1.2 Where no subjects have been enrolled and no additional risks have been identified; or
- 6.1.2.1.3 Where the remaining research activities are limited to data analysis.

6.1.2.2 Category 9: Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

6.2 Expedited Review of Minor Changes to Approved Research

6.2.1 Review of minor changes to research activities for research previously approved during the period of one year or less for which approval is authorized may be completed under Expedited review procedures. Minor changes are those that neither increase risk nor materially change the risk/benefit ratio. CIRB submissions eligible for expedited review may include, but are not limited to the following:

- 6.2.1.1 Study amendments;
- 6.2.1.2 Consent form/parental permission form modifications;
- 6.2.1.3 Study Chair response to stipulations as outlined in the approved pending modification notification;
- 6.2.1.4 Recruitment materials;
- 6.2.1.5 Medical procedures that are added as a change in research and are on the current list of categories that may be reviewed using expedited review located at the following URL: <http://www.hhs.gov/ohrp/policy/expedited98.html>; and
- 6.2.1.6 Annual Signatory Institution Worksheet, Annual Principal Investigator Worksheet, and Study-Specific Worksheet for Signatory Institutions and Principal Investigators using the CIRB as the IRB of Record.

6.3 Administrative Considerations for Expedited Review

6.3.1 The CIRB Chair, Vice Chair, or designee conducts expedited reviews.

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- 6.3.2 In reviewing the research, the reviewer may exercise the authorities described in section 7.5.4.1.
- 6.3.3 The reviewer receives all documents required for the type of review being conducted. These are the same documents required for convened CIRB review.
- 6.3.4 The criteria for approval using the expedited procedure are the same as those for review by a convened IRB. The regulatory criteria for approval of research are described in section 7.2 of these SOPs.
- 6.3.5 The reviewer may elect to forward to the convened CIRB even if the submission meets the criteria for expedited review, but may not disapprove the submission.
- 6.3.6 The reviewer documents that the modifications to previously approved research undergoing review represent “minor” modifications and that the criteria for approval are met.
- 6.3.7 When conducting initial or continuing review of studies using expedited review, the reviewer documents the specific category used for expedited review and the action taken by the reviewer.
 - 6.3.7.1 When conducting initial review of studies using expedited review, the reviewer ensures the regulatory criteria for approval of research are met. The regulatory criteria for approval of research are described in section 7.2 of these SOPs.
 - 6.3.7.2 When conducting continuing review of studies using expedited review, the reviewer ensures the following per the Guidance on IRB Continuing Review of Research located at the following URL:
<http://www.hhs.gov/ohrp/policy/continuingreview2010.html>:
 - 6.3.7.2.1 The determination that no additional risks have been identified.
 - 6.3.7.2.2 Any significant new findings that may be related to the subjects willingness to continue participation are provided to the subject in accordance with 45 CFR 46.116(b)(5) under pre-2018 Requirements and 45 CFR 46.116(c)(5) under 2018 Requirements. If the reviewer identifies new findings that may impact subjects’ willingness to continue participation, the reviewer will consider whether the continuing review

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still qualifies for expedited review or requires review by the convened CIRB.

- 6.3.8 Outcome Letters for expedited reviews include the following:
- 6.3.8.1 A justification for the use of expedited review procedures (including the applicable regulatory citations);
 - 6.3.8.2 Actions taken by the reviewer;
 - 6.3.8.3 Findings required by regulations; and
 - 6.3.8.4 The required elements of all Outcome Letters as listed in Section 5.14.
- 6.3.9 A list of determinations made through the expedited review procedure are included on the agenda for the next convened meeting of the appropriate CIRB and the studies will be made available to individual CIRB members upon request.
- 6.3.10 Since submissions reviewed via expedited review procedures relate to studies that are minimal risk or only include minor changes to previously reviewed research as defined in section 6.2.1, the review of a subject matter consultant is not required for expedited review and approval, even though such a consultant might have been involved in the initial CIRB review. The reviewer may request the subject matter consultant’s review if there are questions requiring their expertise.

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Section 7.0 CIRB Decision-Making

7.1 Independence of CIRB Decision-Making

The independence of the CIRB is crucial to ensure that its decisions are based solely on the protections of study participants. To that end, attendance at CIRB meetings is restricted to CIRB members, support staff, and individuals invited to provide the CIRB with the most up-to-date information about a specific study or issue under review with the CIRB. Observers are strongly discouraged.

The CIRBs' decision-making regarding review of research is independent of NCI, CTEP, and DCP coordinating groups, Study Chairs, and Signatory Institution Principal Investigators.

7.2 Exempt Research

7.2.1 Research involving human subjects is exempt from CIRB review if it fits in any of the following categories per 45 CFR 46.101 under pre-2018 Requirements:

7.2.1.1 Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

7.2.1.2 Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

7.2.1.3 Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under 7.2.1.2, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of

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the personally identifiable information will be maintained throughout the research and thereafter.

- 7.2.1.4 Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- 7.2.1.5 Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.
- 7.2.1.6 Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.
- 7.2.2. Research involving human subjects may be determined to be exempt by the CIRB if it fits in any of the following categories per 45 CFR 46.104 under 2018 Requirements:
 - 7.2.1.1 Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
 - 7.2.1.2 Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public

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behavior (including visual or auditory recording) if at least one of the following criteria is met: (i) the information obtained is recorded in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation; or (iii) the information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by 45 CFR 46.111(a)(7).

7.2.1.3 Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met: (a) the information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects; (b) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or (c) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

7.2.1.3.1 For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

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7.2.1.3.2 If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

7.2.1.4 Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met: (i) the identifiable private information or identifiable biospecimens are publicly available; (ii) information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects; (iii) the research involves only information collection and analysis involving the investigator’s use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of “health care operations” or “research” as those terms are defined at 45 CFR 164.501 or for “public health activities and purposes” as described under 45 CFR 164.512(b); or (iv) the research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

7.2.1.5 Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or

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otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

(i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

7.2.1.6 Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

7.2.3 Requests for exemption from 45 CFR 46 are reviewed and determined by the CIRB following the current expedited review procedures.

7.2.4 Documentation of exemption determination is retained in the CIRB’s files and the Study Chair is notified of the determination.

7.2.5 Studies that do not meet the categories of exemption noted above are forwarded for review by the CIRB.

7.3 Criteria for Approval of Research

7.3.1 The CIRB must determine that the following requirements are satisfied before it approves any research and any review type:

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7.3.1.1 Risks to subjects are minimized by using procedures consistent with sound research design that will yield the expected knowledge; which do not unnecessarily expose subjects to risk; and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes;

7.3.1.2 Risks to subjects are reasonable in relationship to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result;

Note: In evaluating risks and benefits, the CIRB considers only those risks and benefits that may result from the research, as distinguished from risks and benefits of therapies that subjects would receive if not participating in the research. The CIRB 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 [45 CFR 46.111(a)(2)].

7.3.2 Selection of subjects is equitable, taking into account the purposes of the research, the selection (inclusion/exclusion) criteria, and the setting in which the research will be conducted;

7.3.2.1 Information regarding the setting in which the research will be conducted is provided to the CIRB Local Context Subcommittee member as part of the Annual Principal Investigator Worksheet.

7.3.3 Informed consent will be sought from each prospective subject or the subject's legally authorized representative in a language understandable to the prospective subject or representative, in accordance with 45 CFR 46.116 and, when applicable, 21 CFR 50.25;

7.3.3.1 Information regarding the use of legally authorized representatives is provided to the CIRB Local Context Subcommittee member as part of the Annual Principal Investigator Worksheet.

7.3.3.2 *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, *legally authorized representative* means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on

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behalf of the prospective subject to the subject’s participation in the procedure(s) involved in the research.

- 7.3.4 For NCI-sponsored Phase 3 trials, a DSMB is in place to ensure that adequate provisions are included in the research plan for monitoring the data collected to ensure the safety of subjects [per 45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6)].
 - 7.3.4.1 For all other studies, the CIRB will review study-specific safety monitoring procedures considering the following.
 - 7.3.4.1.1 A determination as to whether the safety monitoring is sufficient (in terms of rigor and frequency) given the level of risk of the study;
 - 7.3.4.1.2 The adequacy of the entity that will be monitoring the study;
 - 7.3.4.1.3 The data to be monitored;
 - 7.3.4.1.4 Procedures for analysis and interpretation of the data;
 - 7.3.4.1.5 Action to be taken upon specific events or end points;
 - 7.3.4.1.6 Procedures for communication from the data monitor to the CIRB.
- 7.3.5 Appropriate additional safeguards are included in the study to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence. The CIRB may request additional guidance from members or consultants knowledgeable about or experienced in working with a particular class of vulnerable subjects.
 - 7.3.5.1 Information regarding the specific vulnerable populations that would be potentially enrolled at a local institution is provided to the CIRB Local Context Subcommittee member as part of the Annual Principal Investigator Worksheet.
- 7.3.6 The plans for subject recruitment and retention that involve advertising or other contact with potential subjects are consistent with the protocol, the consent form, and FDA guidelines. There is no payment for participation in coordinating group trials.
 - 7.3.6.1 Information regarding local recruitment processes is provided to the CIRB Local Context Subcommittee member as part of the Annual Principal Investigator Worksheet.
 - 7.3.6.2 Local recruitment material is provided to the CIRB for review using the Annual Signatory Institution Worksheet or Study-Specific Worksheet.

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7.3.7 Informed consent will be appropriately documented in accordance with and to the extent required by 45 CFR 46.117 and 21 CFR 50.27 (when appropriate). A written copy of the consent form is provided to the study participant or legally authorized representative.

7.3.8 Adequate provisions are in place to protect privacy of subjects and to maintain the confidentiality of data, where appropriate.

7.3.8.1 Information regarding the provision in place to protect privacy of potential participants and to maintain the confidentiality of data is provided to the CIRB Local Context Subcommittee member as part the Annual Principal Investigator Worksheet for all Principal Investigators who can open studies with the CIRB.

7.4 Requirements for Informed Consent or Parental Permission

7.4.1 The CIRB has the responsibility for approving a consent form or parental permission form unless waived in accordance with 45 CFR 46.116(d) under pre-2018 Requirements and 45 CFR 46.116(f) under 2018 Requirements.

7.4.1.1 Informed Consent must be documented by the use of a written consent form approved by the CIRB unless documentation is waived by the CIRB as provided in 45 CFR 46.109(c), 46.117, and, when applicable, 21 CFR 56.109(c). A copy of the consent form is provided to the potential study participant or representative.

7.4.1.2 The consent form must be a written consent document that embodies the elements of informed consent required by 45 CFR 46.116 and 46.117(b)(1) and, when applicable, 21 CFR 50.25 and 50.27(b)(1).

7.4.1.3 The consent form must be written so that it does not include any exculpatory language through which the subject or the representative 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 as stated in 45 CFR 46.116 and 21 CFR 50.20.

7.4.2 Basic elements of consent form include the following elements per 45 CFR 46.116(a) under pre-2018 Requirements, 45 CFR 46.116(b) under 2018 Requirements, and 21 CFR 50.25(a) for FDA-regulated studies:

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- 7.4.2.1 Statement that the study involves research.
- 7.4.2.2 Explanation of the purposes of the research.
- 7.4.2.3 Expected duration of the subject's participation in the research.
- 7.4.2.4 Description of the procedures to be followed.
- 7.4.2.5 Identification of any procedure that is experimental.
- 7.4.2.6 Description of any reasonably foreseeable risks or discomforts to the subject.
- 7.4.2.7 Description of any benefits to the subject or to others, which may reasonably be expected from the research.
- 7.4.2.8 Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- 7.4.2.9 Statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, and if applicable, a statement of the possibility that the Food and Drug Administration may inspect the records.
- 7.4.2.10 For research involving more than minimal risk, an explanation as to whether any compensation is available if injury occurs, whether any medical treatments are available if injury occurs, and if so, what they consist of, or where further information can be obtained.
- 7.4.2.11 Explanation of whom to contact for answers to pertinent questions about the research, research subject's rights, and whom to contact in the event of a research-related injury to the subject or if the subject has concerns or complaints about the research.
- 7.4.2.12 Statement that participation is voluntary, that refusal to participate involves no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- 7.4.2.13 Under 2018 Requirements (45 CFR 46.116(a)(5)), the following is required:

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(i) Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative 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.

(ii) 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 prospective subject’s or legally authorized representative’s understanding of the reasons why one might or might not want to participate.

7.4.3 When appropriate, one or more of the following additional elements of information shall also be provided to each subject per 45 CFR 46.116(b) under pre-2018 Requirements, 45 CFR 46.116(c) under 2018 Requirements (includes sections 7.4.3.7 through 7.4.3.9), and 21 CFR 50.25(b) for FDA-regulated studies:

7.4.3.1 Statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

7.4.3.2 Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent.

7.4.3.3 Any additional costs to the subject that may result from participation in the research.

7.4.3.4 Consequence of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject.

7.4.3.5 Statement that significant new findings developed during the course of the research, which may relate to the subject’s willingness to continue, will be provided to the subject.

7.4.3.6 Approximate number of subjects involved in the study.

7.4.3.7 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;

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- 7.4.3.8 A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
- 7.4.3.9 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 genome or exome sequence of that specimen).
- 7.4.3.10 When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in consent forms and processes. The statement is: "A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."
- 7.4.4 Consent Form Review for Local Context Considerations
 - 7.4.4.1 Boilerplate language and other institutional requirements that are incorporated into the consent form for NCI studies to address local context consideration are provided to the CIRB for review as part of the Annual Signatory Institution Worksheet.
 - 7.4.4.2 Boilerplate language and other institutional requirements are reviewed and approved by the CIRB Local Context Subcommittee members. All boilerplate language and other institutional requirements must comply with the requirements as listed in Sections 7.3 and 7.4.
 - 7.4.4.3 Approval letters from the CIRB include the approved boilerplate language and other institutional requirements and instructions that the Principal Investigator is responsible for the incorporation of this language into the CIRB-approved version of the consent form posted on the CIRB website.
 - 7.4.4.4 The content of the CIRB-approved model consent form cannot be altered, except for incorporation of CIRB-approved boilerplate language as described above.
- 7.4.5 The CIRB may require that information in addition to that required in Federal regulations is given to research subjects when in its judgment the

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information would meaningfully add to the protection of the rights and welfare of subjects.

7.4.6 Waiver of Documentation of Consent

7.4.6.1 Because of the nature of the research reviewed by the CIRBs, it is not anticipated that the CIRB will waive documentation of consent. The process is included here for completeness.

7.4.6.2 The CIRB, for some or all subjects, may waive the requirement that the subject or the subject’s representative sign a written consent document if it finds any of the following based on pre-2018 Requirements:

7.4.6.2.1 The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject’s wishes will govern;

7.4.6.2.1 The research presents no more than minimal risk of harm to subjects, and

7.4.6.2.2 The research involves no procedures for which written consent is normally required outside the research context.

7.4.6.3 The CIRB, for some or all subjects, may waive the requirement that the subject or the subject’s representative sign a written consent document if it finds any of the following under 2018 Requirements:

7.4.6.3.1 The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from breach of confidentiality. In these cases, each subject will be asked whether the subject wants documentation linking the subject with the research and the subjects wishes will govern (45 CFR 46.117(c)(1)). This option does not apply to research activity that is regulated by the FDA.

7.4.6.3.2 The research presents no more than minimal risk of harm to subjects, and involves no procedures for which written consent is normally required outside the research context. The CIRB may still require the investigator to provide subjects with a written

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statement regarding the research (45 CFR 46.117(c)(2), 21 CFR 56.109(c)(1) and (d)).

- 7.4.6.3.3 If the subjects or legally authorized representatives 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.

Note: If the CIRB waives the requirement of documentation of informed consent as identified above, the CIRB will review a written statement or script of the information that will be provided to subjects in order to secure their consent. The CIRB will consider requiring the investigator to provide participants with a written statement regarding the research.

Note: For research under DHHS jurisdiction, but not FDA jurisdiction, the CIRB may waive the requirement for a signed written consent document if the only link between the subject and the research would be the consent form and the principal risk is harm from a breach of confidentiality.

7.4.7 Waiver of Consent or Parental Permission

7.4.7.1 The CIRB may consider a waiver of consent or parental permission for research not under the jurisdiction of the FDA Regulations 21 CFR Parts 50 and 56. For such research, the CIRB may waive consent or parental permission only after considering the criteria for waiving consent or parental permission at 45 CFR 46.116(f)(3), which are:

- 7.4.7.1.1 The research involves no more than minimal risk to subjects,
- 7.4.7.1.2 The waiver or alteration will not adversely affect the rights and welfare of the subjects,
- 7.4.7.1.3 If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format (applicable for 2018 Requirements only),
- 7.4.7.1.4 The research could not practicably be carried out without the waiver or alteration, and
- 7.4.7.1.5 Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

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7.4.7.2 The CIRB may consider a waiver of consent or parental permission for research involving in vitro diagnostic device studies using leftover human specimens that are not individually identifiable outlined in the FDA guidance titled Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable - Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff issued April 25, 2006 and located at the following URL:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078384.htm>.

7.4.7.3 Under the 2018 Requirements, the CIRB may approve research in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective participants without the informed consent of the prospective participant or the participant’s legally authorized representative, if either of the following conditions are met:

7.4.7.3.1 The investigator will obtain information through oral or written communication with the prospective participant or legally authorized representative, or

7.4.7.3.2 The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

7.4.8 Consent at Age of Majority

7.4.8.1 For study participants who begin participation in a study as minors and who reach the age of majority, as determined by state law, the CIRB requires consent of the study participant be obtained per local institution policies and procedures as described in the Annual Signatory Institution Worksheet upon reaching age of majority.

7.4.9 Consent Forms for Multiphase Trials

7.4.9.1 For multiphase trials (i.e. phase 1/2 and phase 2/3), a Study Chair may present the CIRB with consent forms for both phases of the trial at initial review either as a single consent form or as separate consent forms for each phase. In either case, the CIRB requires that the Study Chair ensure that the consent form for the next phase is appropriately updated based on any findings in the first phase of the trial.

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7.5 Research Involving Vulnerable Populations, Pregnant Women, Human Fetuses, and Neonates

When reviewing, studies involving vulnerable subjects, the CIRB evaluates whether additional safeguards (beyond the requirements for approval of research noted in 45 CFR 46.111 and 21 CFR 56.111) are needed using the appropriate reviewer worksheet. Vulnerable subjects include, but are not limited to, , children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged person.

7.5.1 Criteria for Approval of Research Involving Pregnant Women, Human Fetuses, and Neonates per Subpart B

7.5.1.1 When the CIRB considers research involving pregnant women and fetuses, it ensures that:

7.5.1.1.1 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;

7.5.1.1.2 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 which cannot be obtained by any other means;

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

7.5.1.1.4 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 the informed consent provisions of 45 CFR 46 Subpart A;

7.5.1.1.5 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 45 CFR 46 Subpart A,

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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;

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

7.5.1.1.7 For children who are pregnant, assent and permission are obtained in accordance with the provisions of 45 CFR 46 Subpart D and/or 21 CFR 50, Subpart D.

7.5.1.2 The CIRB requires confirmation that the requirements of 45 CFR 46.204 are satisfied on the Annual Principal Investigator Worksheet:

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

7.5.1.2.2 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

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

7.5.1.3 When the CIRB considers research involving neonates, it ensures:

7.5.1.3.1 Neonates of uncertain viability may be involved in research if all the following conditions are met:

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

b. The CIRB 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

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iii. 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 legally authorized representative is obtained in accord with 45 CFR 46 Subpart A, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

7.5.1.4 The CIRB requires confirmation that individuals engaged in the research will have no part in determining the viability of a neonate. This confirmation is provided as part of the Annual Principal Investigator Worksheet.

7.5.1.5 Nonviable neonates may not be involved in research unless all the following additional conditions are met:

7.5.1.5.1 Vital functions of the neonate will not be artificially maintained;

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

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

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

7.5.1.5.5 The legally effective informed consent of both parents of the neonate is obtained in accord with 45 CFR 46, Subpart A, 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 will suffice, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

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7.5.1.6 A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of 45 CFR 46 Subparts A and D.

7.5.1.7 The CIRB does not review research under 45 CFR 46.207 (research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates).

7.5.1.8 The CIRB Operations Office and Chair ensure that the appropriate determinations are made and documents as required in the minutes.

7.5.2 Criteria for Approval of Research Involving Children

7.5.2.1 When the CIRB reviews research involving children, the CIRB determines into which of the following four risk/benefit categories the research fits. The CIRB’s designation is recorded in the minutes for that meeting. The four possible categories are:

7.5.2.1.1 Research not involving greater than minimal risk (45 CFR 46.404 and 21 CFR 50.51).

- a. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- b. The CIRB must determine that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 45 CFR 46.408 and 21 CFR 50.55.

7.5.2.1.2 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405 and 21 CFR 50.52). For this category of research to be approved, the CIRB must find that:

- a. The risk is justified by the anticipated benefits to the subjects.

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- b. The relation of the anticipated benefit to the risk must be at least as favorable to the subjects as that presented by available alternative approaches.
- c. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408 and 21 CFR 50.55.

7.5.2.1.3 Research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject’s disorder or condition (45 CFR 46.406 and 21 CFR 50.53). For this category of research to be approved, the CIRB must find:

- a. The risk represents a minor increase over minimal risk.
- b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.
- c. The intervention or procedure is likely to yield generalizable knowledge about the subject’s disorder or condition, which is of vital importance for the understanding or amelioration of the subject’s disorder or condition.
- d. Adequate provisions are made for soliciting the permission of both parents of each child unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

7.5.2.1.4 Research not fitting into any of the categories outlined above, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children cannot be performed without review by the Secretary of DHHS as outlined in 45 CFR 46.407 and the Commissioner of the FDA, when applicable, as outlined in 21 CFR 50.54.

7.5.2.2 The CIRB will consider additional safeguards for children on a study-by-study basis.

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7.5.2.3 Age of Assent

- 7.5.2.3.1 Overview: In all cases, regardless of whether the CIRB requires assent, the CIRB expects investigators to provide children with developmentally appropriate information about their diagnosis, treatment, and proposed research participation. In particular, investigators should explain the purpose as well as the incremental procedures, risks and benefits of the clinical trial, and offer an opportunity to ask questions.
- 7.5.2.3.2 The CIRB does not require that the signature of the child be obtained. Information regarding local institutional policies regarding documentation of assent is provided to the CIRB Local Context Subcommittee member as part the Annual Principal Investigator Worksheet for all Principal Investigators who can open studies with the CIRB.
- 7.5.2.3.3 For children under 7 years of age, the assent of the child is not a necessary condition for participating in a research protocol.
- 7.5.2.3.4 For children 14 years of age or older, the assent of the child is a necessary condition for participating in the research. Principal Investigators, however, may request that assent be waived *for an individual child*, because the capability of that child is so limited that they cannot reasonably be consulted [45 CFR 46.408(a)].
- 7.5.2.3.5 Children age 7 through 13 vary considerably in their development and cognitive capacity. Many of these children have limited ability to participate in decision making, and a formal request for assent will not be appropriate. Nonetheless, for all protocols, CIRB expects investigators to provide to children in this age range developmentally appropriate information about their diagnosis, treatment, and proposed research participation. In particular, investigators should explain the purpose as well as the incremental procedures, risks and benefits of the clinical trial, and offer an opportunity to ask questions.
 - a. For protocols not involving greater than minimal risk (45 CFR 46.404 and 21 CFR 50.51), or involving greater than minimal risk and no

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prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition for which there is no expected direct therapeutic benefit (45 CFR 46.406 and 21 CFR 50.53), the assent of children ages 7 and older is a necessary condition for participating in the research. Principal Investigators, however, may request that assent be waived *for an individual child*, because the capability of that child is so limited that they cannot reasonably be consulted [45 CFR 46.408(d)].

- b. For protocols involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405 and 21 CFR 50.52), the formal assent of children below age 14 is not a necessary condition to proceeding with enrollment. Investigators may decide that assent is appropriate for an individual child, based on an individual assessment of capacity.
- c. Nothing in this policy precludes such assent. Additionally, local IRBs with policies to obtain assent from children at an age below 14 may choose to follow their own requirements.

7.5.2.3.6 In limited and specific circumstances, assent can be waived under 46.408 if “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.” These waivers are only appropriate when the study intervention is likely to be more effective than other treatments available outside the trial and should only apply to those components that are judged more beneficial (thus assent may be sought for non-therapeutic components).

7.5.2.3.7 In limited and specific circumstances, assent can be waived under 21 CFR 50.55(d) if “The research involves no more than minimal risk; and the waiver or alteration will not adversely affect the rights and welfare of the subjects; and the research could not be practicably carried out without the waiver or alteration, and whenever appropriate the subjects will be provided with additional pertinent information after participation.”

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7.5.2.4 The CIRB requires the permission of a child’s parent(s) or legal guardian(s) based on the risk level of the research as described in 45 CFR 46.408 and, when applicable, 21 CFR 50.55.

7.5.2.4.1 Permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 or 46.405, and, when applicable, 21 CFR 50.51 and 50.52.

7.5.2.4.2 Permission of both parents is required for research to be conducted under 45 CFR 46.406 and 46.407, and, when applicable, 21 CFR 50.53 and 50.54, unless one parent is deceased, unknown, incompetent, not reasonably available, or in the case where only one parent has legal responsibility for the care and custody of the child.

7.5.3 Review of Research Involving the Economically or Educationally Disadvantaged

7.5.3.1 The CIRB considers any additional safeguards that would be required to permit economically or educationally disadvantaged persons to participate in a study.

7.5.4 Review of Research Involving Prisoners

7.5.4.1 The CIRB is not constituted to review research for the inclusion of prisoners.

7.5.5 Individuals with Impaired Decision-Making Capacity

7.5.5.1 Research involving subjects with impaired decision-making capacity warrants special attention. Persons with impaired decision-making capacity must not be subjects in research simply because they are readily available nor should they be excluded solely based on impairment unless their impairment may result in increased risk.

7.5.5.2 When the CIRB reviews research that includes subjects with impaired decision-making capacity, the CIRB should have or acquire knowledge about this population or experience working with this population (45 CFR 46.107).

7.5.5.3 Research involving persons with impaired decision-making capacity may only be approved by the CIRB when all the following conditions apply:

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7.5.5.3.1 The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to directly benefit that subject.

7.5.5.3.2 The assent of the subject with impaired decision-making capacity is obtained whenever the subject is capable of providing assent.

7.5.5.4 The CIRB reviews the protocol to determine whether there are sufficient safeguards to protect the rights and welfare of subjects with impaired decision-making capacity (45 CFR 46.111(b) and, when applicable, 21 CFR 56.111(b).

7.5.5.5 The CIRB reviews procedures described in the Annual Principal Investigator Worksheet related to:

7.5.5.5.1 Determining whether inclusion of subjects who lack capacity to consent for themselves is allowed under local law (45 CFR 46.111);

7.5.5.5.2 Evaluating the mental status of prospective subjects to determine whether they are capable of consenting; and

7.5.5.5.3 Ensuring that persons providing surrogate consent for these subjects have the legal authority to give such consent.

7.5.5.6 If the research involves a clinical condition that could lead to impaired decision-making capacity, the CIRB should consider whether sufficient safeguards are in place to protect the rights and welfare of subjects who become decision-impaired.

7.6 CIRB Actions

7.6.1 All CIRB actions may apply to all types of submissions submitted for review by the CIRB.

7.6.2 For each review, the CIRB takes a single action.

7.6.3 Actions may be taken by an expedited reviewer or the convened CIRB.

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7.6.4 CIRB Actions and Definitions

7.6.4.1 The following actions may be taken by an expedited reviewer or by the convened CIRB:

7.6.4.1.1 **Approve:** The CIRB approves research when it determines that the regulatory and CIRB SOP requirements are met. The CIRB is approving the research to begin or continue as written per the current Protocol Version Date. As a condition of approval translated versions of CIRB-approved documents may be submitted and approved by the CIRB Operations Office per Sections 5.9.9 and 8.9.1 of this SOP.

7.6.4.1.2 **Approve pending modification(s):** The CIRB approves research pending modification when it determines that the regulatory and CIRB SOP requirements for approval are met, but the CIRB requests modifications. The CIRB may approve pending modification if it determines that the regulatory and CIRB SOP requirements can be met by way of specific changes directed by the CIRB.

7.6.4.1.3 **Approve with query(ies):** The CIRB approves research with query when it determines that the regulatory and CIRB SOP requirements for approval are met, no modifications are required, and the CIRB requests information that does not impact participant safety or any determinations of the CIRB. The regulatory and CIRB criteria for approval are met without the requested information. The CIRB is approving the research to begin or continue as written per the current Protocol Version Date.

7.6.4.2 The following actions may be taken only by the convened CIRB:

7.6.4.2.1 **Table:** The CIRB tables research when the regulatory and CIRB SOP criteria for approval are not met, but the study can be revised to meet the criteria. The CIRB also tables research when there is insufficient information to determine whether the regulatory and SOP requirements for approval are met.

7.6.4.2.2 **Disapprove:** The CIRB disapproves research when it determines that the regulatory and CIRB SOP requirements for approval cannot be met.

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- 7.6.4.2.3 Suspend Accrual: The CIRB suspends accrual when it determines that continuing accrual could threaten the safety or well-being of potential study participants.
- 7.6.4.2.4 Suspend Study Intervention: The CIRB suspends study intervention when it determines that continuing the intervention could threaten the safety or well-being of study participants.
- 7.6.4.2.5 Suspend Approval of Research: The CIRB temporarily suspends approval of research when it determines that continuing research activities could threaten the safety or well-being of study participants or when research is not being conducted in accordance with the CIRB’s requirements.
- 7.6.4.2.6 Terminate Approval of Research: The CIRB permanently terminates approval of research when it determines that the research irreparably and adversely affects the safety or well-being of study participants or when research is not being conducted in accordance with the CIRB’s requirements.
- 7.6.4.2.7 Lift Suspension: The CIRB lifts any type of suspension when it determines that the safety or well-being of study participants is no longer threatened.

7.6.5 Specific Considerations based on CIRB Action

7.6.5.1 Approve

- 7.6.5.1.1 The CIRB may approve research for a maximum of one year but may approve for any period of time less than one year commensurate with the foreseeable risks of the research.
- 7.6.5.1.2 The CIRB will continue to conduct continuing review for all studies under its purview.

7.6.5.2 Approve pending modification(s)

- 7.6.5.2.1 The Protocol Version Date for which this action is taken may not be implemented until the CIRB approves the research.
- 7.6.5.2.2 Submitted modifications required by the convened CIRB may be confirmed and approved by expedited review.
- 7.6.5.2.3 Modifications in addition to those required by the CIRB may be submitted with the Study Chair’s

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response to the CIRB, except when the study is undergoing initial review.

7.6.5.2.4 No approval period is established.

7.6.5.3 Approve with query(ies)

7.6.5.3.1 Response is not required from the Study Chair, but should a response be submitted to the CIRB it may be reviewed by expedited procedures.

7.6.5.3 Table

7.6.5.3.1 The Protocol Version Date for which this action is taken may not be implemented until the CIRB approves the research.

7.6.5.3.2 No approval period is established.

7.6.5.3.3 The response from the Study Chair is expected and may only be reviewed by the convened CIRB.

7.6.5.4 Disapprove

7.6.5.4.1 When the CIRB disapproves a new study it is rejecting the research as submitted.

7.6.5.4.2 If the Study Chair wants to revise the study, it must be resubmitted as a new study.

7.6.5.4.3 When the CIRB votes to disapprove a change in research, the change cannot be implemented but the research may continue as previously approved by the CIRB.

7.6.5.4.4 No response from the Study Chair is required.

7.6.5.4.5 The CIRB will take no further action regarding the research, or change in research, as submitted.

7.6.5.5 Suspend Study Accrual

7.6.5.5.1 A conference call including the CIRB Chair, accompanied by other CIRB members, and the Study Chair, coordinating group leadership, CTEP or DCP leadership, CIB Disease Therapeutic Heads, and when appropriate DSMB representatives is required to ensure the CIRB has the most current information upon which to base their decision. The individuals and their roles are outlined below:

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- a. The Study Chair provides the CIRB with study-specific information upon which to base its decision.
- b. The coordinating group leadership provides the CIRB with study-specific information as well as a broader perspective and information pertaining to actions taken by the coordinating group on similar issues.
- c. The CTEP/DCP and CIB representatives provide the CIRB with their perspective and with information regarding how similar concerns are addressed across all trials.
- d. DSMB representatives may be asked to provide their perspective and information on DSMB actions and its assessment of data.

7.6.5.5.2 If a conference call cannot be scheduled during the CIRB meeting, the CIRB Chair, accompanied by other CIRB members, must conference with the above individuals prior to or after the CIRB meeting.

7.6.5.5.3 A vote to suspend accrual will not be taken until the conference call has occurred. The vote must occur in a timely manner and should occur within two weeks of the conference call.

7.6.5.5.4 Before the CIRB suspends accrual, the CIRB considers actions to protect the rights and welfare of enrolled participants. Where the suspension of accrual could harm subjects further, the CIRB will consider alternative actions.

7.6.5.5.5 If the CIRB votes to suspend accrual:

- a. Accrual remains suspended until the CIRB votes to lift suspension of accrual.
- b. Enrolled participants should continue per the protocol.
- c. The Study Chair must continue to fulfill the requirements for continuing review approval.
- d. The CIRB discusses with the Study Chair, coordinating group leadership, CTEP or DCP leadership, CIB Disease Therapeutic Heads, and when appropriate DSMB representatives whether and how current study participants, investigators, and/or IRBs should be informed of the suspension of accrual.

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- e. The Study Chair must submit a response to the CIRB review, in a timely manner.

7.6.5.6 Suspend Study Intervention

7.6.5.6.1 A conference call including the CIRB Chair, accompanied by other CIRB members, and the Study Chair, coordinating group leadership, CTEP or DCP leadership, CIB Disease Therapeutic Heads, and DSMB representatives is required to ensure the CIRB has the most current information upon which to base their decision. The role of each participant is outlined below:

- a. The Study Chair provides the CIRB with study-specific information, including any adverse events or outcomes, upon which to base its decision.
- b. The coordinating group leadership provides the CIRB with study-specific information as well as a broader perspective and information pertaining to actions taken by the coordinating group on this or similar issues.
- c. The CTEP/DCP and CIB representatives provide the CIRB with their perspective and with information regarding how similar concerns are addressed across all trials.
- d. DSMB representatives may be asked to provide their perspective and information on DSMB actions and its assessment of data.

7.6.5.6.2 If a conference call cannot be scheduled during the CIRB meeting, the CIRB Chair, accompanied by other CIRB members, must conference with the above individuals prior to or after the CIRB meeting.

7.6.5.6.3 A vote to suspend study intervention will not be taken until the conference call has occurred. The vote must occur in a timely manner and should occur within two weeks of the conference call.

7.6.5.6.4 Before the CIRB suspends study intervention, the CIRB considers actions to protect the rights and welfare of enrolled study participants. Where the suspension of study intervention could harm subjects further, the CIRB will consider alternative actions.

7.6.5.6.5 If the CIRB votes to suspend study intervention:

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- a. The study intervention remains suspended until the CIRB votes to lift suspension of study intervention.
- b. The Study Chair must continue to fulfill the requirements for continuing CIRB review approval since participants remain on study.
- c. The CIRB discusses with the Study Chair, coordinating group leadership, CTEP or DCP leadership, CIB Disease Therapeutic Heads, and DSMB representatives whether and how current study participants, investigators, and/or IRBs should be informed of the suspension of study intervention. Any information sent to research participants requires CIRB review.
- d. The Study Chair must submit a response, in a timely manner, containing revisions that enable the study to proceed safely.

7.6.5.7 Suspend Approval of Study

7.6.5.7.1 A conference call including the CIRB Chair, accompanied by other CIRB members, and the Study Chair, coordinating group leadership, CTEP or DCP leadership, CIB Disease Therapeutic Heads, , and DSMB representatives is required to ensure the CIRB has the most current information upon which to base their decision. The role of each participant is outlined below:

- a. The Study Chair provides the CIRB with study-specific information upon which to base its decision.
- b. The coordinating group leadership provides the CIRB with study-specific information as well as a broader perspective and information pertaining to actions taken by the coordinating group on this or similar issues.
- c. The CTEP/DCP and CIB representatives provide the CIRB with their perspective and with information regarding how similar concerns are addressed across all trials.
- d. DSMB representatives may be asked to provide their perspective and information on DSMB actions and its assessment of data.

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- 7.6.5.7.2 If a conference call cannot be scheduled during the CIRB meeting, the CIRB Chair, accompanied by other CIRB members, must conference with the above individuals prior to or after the CIRB meeting.
- 7.6.5.7.3 A vote to suspend approval of research will not be taken until the conference call has occurred. The vote must occur in a timely manner and should occur within two weeks of the conference call.
- 7.6.5.7.4 Before the CIRB suspends approval of research, the CIRB considers actions to protect the rights and welfare of enrolled study participants. Where the suspension of the approval of the research could harm subjects further, the CIRB will consider alternative actions.
- 7.6.5.7.5 If the CIRB votes to suspend approval of research:
 - a. The study remains suspended until the CIRB votes to lift suspension of approval of research.
 - b. The CIRB notifies the following offices within 21 days, of the CIRB’s determination when there is a suspension of CIRB approval:
 - i. Director of the DCTD
 - ii. Associate Director of CTEP or Deputy Director, DCP
 - iii. OHRP
 - iv. FDA, when applicable
 - c. The Study Chair must continue to fulfill the requirements for continuing CIRB review approval.
 - d. The CIRB discusses with the Study Chair, coordinating group leadership, CTEP or DCP leadership, CIB Disease Therapeutic Heads, and DSMB representatives whether and how current study participants, investigators, and/or IRBs should be informed of the suspension of approval. Any information sent to research participants requires CIRB review.
 - e. The Study Chair must submit a response, in a timely manner, containing revisions that enable the study to proceed safely.

7.6.5.8 Lift Suspension

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7.6.5.8.1 Lifting suspension of accrual, study intervention, or approval of research is appropriate when:

- a. The concerns that resulted in the suspension have been resolved to the satisfaction of the CIRB; or
- b. An acceptable plan for resolution has been submitted and approved by the CIRB.

7.6.5.9 Terminate Approval of a Study

7.6.5.9.1 A conference call including the CIRB Chair, accompanied by other CIRB members, and the Study Chair, coordinating group leadership, CTEP or DCP leadership, CIB Disease Therapeutic Heads, and DSMB representatives is required to ensure the CIRB has the most current information upon which to base their decision. The role of each participant is outlined below:

- a. The Study Chair provides the CIRB with study-specific information, including any adverse events or outcomes, upon which to base its decision.
- b. The coordinating group leadership provides the CIRB with study-specific information as well as a broader perspective and information pertaining to actions taken by the coordinating group on this or similar issues.
- c. The CTEP/DCP and CIB representatives provide the CIRB with their perspective and with information regarding how similar concerns are addressed across all trials.
- d. DSMB representatives may be asked to provide their perspective and information on DSMB actions and its assessment of data.

7.6.5.9.2 If a conference call cannot be scheduled during the CIRB meeting, the CIRB Chair, accompanied by other CIRB members, must conference with the above individuals prior to or after the CIRB meeting.

7.6.5.9.3 A vote to terminate will not be taken until the conference call has occurred. The vote must occur in a timely manner and should occur within two weeks of the conference call.

7.6.5.9.4 Before the CIRB terminates approval of the study the CIRB considers actions to protect the rights and

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welfare of enrolled study participants. Where the termination could harm subjects further, the CIRB will consider alternative actions.

7.6.5.9.5 If the CIRB votes to terminate approval of research:

- a. The CIRB notifies the following offices within 21 days of the CIRB’s determination when there is a termination of CIRB approval:
 - i. Director of the DCTD or Deputy Director, DCP
 - ii. Associate Director of CTEP or DCP
 - iii. OHRP
 - iv. FDA, when applicable.
- b. The CIRB discusses with the Study Chair, coordinating group leadership, CTEP or DCP leadership, CIB Disease Therapeutic Heads, and DSMB representatives whether and how current study participants, investigators, and or IRBs should be informed of the termination of approval. Any information sent to research participants requires CIRB review.

7.7 Review of Research Involving Adolescents and Young Adults

7.7.1 Adult CIRBs and CPC CIRB

7.7.1.1 The Adult CIRBs and CPC CIRB will make the following determinations for studies for which adolescents are eligible, with the input of a subject matter consultant at the time of initial and subsequent reviews:

7.7.1.1.1 A determination regarding Pediatric Risk Assessments according to 45 CFR 46 Subpart D and, when applicable, 21 CFR 50 Subpart D.

7.7.1.1.2 A determination regarding the age of assent and parental permission according to 45 CFR 46 Subpart D and, when applicable, 21 CFR 50 Subpart D and the CIRB policy regarding age of assent and parental permissions.

7.7.2 Pediatric CIRB

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7.7.2.1 No additional regulatory determinations are required by the Pediatric CIRB for review of studies involving young adults. Subject matter consultants should consider the young adult’s specific needs when reviewing the study.

7.8 Inclusion of Individuals who do not Speak English

7.8.1 Translation of Consent Forms

7.8.1.1 The Clinical Trials Support Unit (CTSU) provides Spanish translations of the CIRB-approved model consent forms for NCTN and select NCORP studies. The translated model consent form is reviewed and approved by the CIRB according to section 5.9.9 and 8.9 of these SOPs. The CIRB Operations Office makes the translations and documentation of approval available to institutions via the CTSU website.

7.8.1.2 Institutions enrolled in the CIRB initiative are encouraged to submit a Spanish translation of boilerplate language for the consent form as part of the Annual Signatory Institution Worksheet so that Principal Investigators at that institution may use the CIRB-approved translated boilerplate and model consent form.

7.8.1.3 Principal Investigators may opt to submit translations of the consent form in languages other than Spanish as part of their Study-Specific Worksheet per section 8.13.2 of these SOPs.

7.8.2 Use of Short Form Consent

7.8.2.1 Principal investigators may use short form consent forms for the study according to the following:

7.8.2.1.1 The Signatory Institution has policies or procedures for use of short form consent forms and has reported these policies or procedures via the Annual Signatory Institution Worksheet or Annual Principal Investigator Worksheet.

7.8.2.1.2 The Signatory Institution has translated short forms available and provides the short forms for CIRB review via the Annual Signatory Institution Worksheet or Study-Specific Worksheet.

7.8.2.1.3 If the Signatory Institution does not have translated short forms available, the Principal Investigator may

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obtain CIRB-approved short forms from the CIRB or CTSU website.

7.8.3 Participant Directed Instruments

7.8.3.1 When a protocol includes Patient Reported Outcomes (PROs) as a primary aim of the study, the protocol should indicate the following:

7.8.3.1.1 Languages in which the instrument is available, as well as information on how to obtain copies in these languages, and

7.8.3.1.2 The eligibility criteria should restrict participation to participants who speak these languages.

Translations of these documents are to be provided by the coordinating group for CIRB review. The CIRB will not review translations provided by Principal Investigators as part of the CIRB’s review of local context considerations.

For validated instruments that are available in languages other than English, the CIRB’s approval of the English instrument as part of its review of a study is considered to extend to the validated translated versions.

7.8.3.2 When a protocol includes Patient Reported Outcomes (PROs) that are not related to a primary aim of the study, completion of the PRO must be optional for all study participants. The protocol should still indicate the languages in which the instrument is available as well as information on how to obtain copies in these languages per section 7.8.3.1.1 above.

Translations of these documents are to be provided by the coordinating group for CIRB review. The CIRB will not review translations provided by Principal Investigators as part of the CIRB’s review of local context considerations.

For validated instruments that are available in languages other than English, the CIRB’s approval of the English instrument as part of its review of a study is considered to extend to the validated translated versions.

7.8.3.3 Ad hoc translation of PROs (site-specific translations or verbal translations) is not permitted. Verbal administration of PROs for the visually impaired is not prohibited if the instrument and

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verbal administration of the instrument is conducted in a language understandable to the participant.

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Section 8.0 CIRB-Decision Making: Specific Considerations Based on Review Type

8.1 Initial Review

8.1.1 Approval Period

The approval period begins when the CIRB approves the initial review of the study.

8.1.2 Study Leader Financial Conflict of Interest

8.1.2.1 Study leaders are defined as personnel who have a primary role in the oversight, design or conduct of the research or have a role in the analysis or management of the data.

8.1.2.2 Thresholds for Financial Conflicts of Interest for Study Leaders

8.1.2.2.1 Financial interests, for a sponsor other than NCI, the product, or service being tested, (see 21 CFR 54.2(f)) below \$5,000 do not need to be disclosed to the CIRB for study leaders, their spouses, and dependent children.

8.1.2.2.2 Financial interests, for a sponsor other than NCI, the product, or service being tested, above about \$5,000 and below \$25,000 are managed by the Group and must be disclosed to the CIRB for study leaders, their spouses, and dependent children. If the Group maintains that an individual's conflict of interest should not disqualify her/him from a leadership position in the study, then a Conflict of Interest Management Plan must be submitted with the CIRB Application. The management plan needs to describe how data collection and analysis will not be biased.

8.1.2.2.3 Financial interests, for a sponsor other than NCI, the product, or service being tested, above \$25,000 for study leaders, their spouses, and dependent children must be disclosed to the CIRB with a Conflict of Interest Management Plan.

8.1.2.3 The NCI CIRB Application for Treatment Studies and the NCI CIRB Application for Continuing Review request information regarding the Study Chair/Study Leaders financial conflicts of interest.

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8.1.2.4 The coordinating group is requested to provide a management plan for any disclosures.

8.2 Study Chair Response

8.2.1 Study Chairs respond to the CIRB requirement for modifications to studies. Study Chair responses are limited to changes required by the CIRB as outlined in its queries, stipulations, or recommendations.

8.2.2 If the CIRB Chair, Vice Chair, or designated reviewer determines the Study Chair Response adequately addresses the CIRB’s requirements as well as all regulatory requirements for approval, the response may be reviewed and approved under expedited review procedures provided that the changes made qualify for expedited review per section 6.0 of these SOPs.

8.2.3 If a Study Chair Response declines changes required by the convened CIRB, the response may be reviewed under expedited review procedures if the CIRB Chair, Vice Chair, or designated reviewer determines that there is sufficient justification for declining to make the requested change and the changes made qualify for expedited review per section 6.0 of these SOPs. The reviewer may request that the response be forwarded to the convened CIRB for review, or may move forward with expedited review of the response but request that the convened CIRB be notified of the response declining to make a requested change.

8.3 Review of Amendments (Changes in Research)

8.3.1 Study Chairs are required to submit to the CIRB two types of changes in research:

8.3.1.1 Amendments in response to CIRB-requested changes

8.3.1.2 Amendments not in response to CIRB-requested changes

8.3.2 During the review of any changes in research, the CIRB considers whether the change involves significant new findings that might relate to a participant's willingness to continue participation. If the CIRB determines that the change includes such findings, the CIRB will consult the Study Chair for additional information and plans to inform study participants and should consider whether the findings constitute an unanticipated problem.

8.3.3 Changes in research cannot be initiated without CIRB approval.

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8.3.4 Only changes in research to eliminate apparent immediate hazards to the participants may be initiated without CIRB approval. These changes must be promptly reported (within 30 days) to the CIRB. The CIRB will determine:

8.3.4.1 Whether the change was reported promptly,

8.3.4.2 Whether the change was consistent with ensuring the participants' continued welfare,

8.3.4.3 If not reported promptly, and not consistent with ensuring the participants' continued welfare, the CIRB will determine whether the implementation of the change without CIRB approval constituted serious noncompliance, and

8.3.4.4 Whether the events precipitating the need for the changes in research constitute an unanticipated problem.

8.3.5 Amendments submitted in response to a CTEP Request for Rapid Amendment (RRA) and Type II action letters follow the same procedures for amendment reviews as outlined above. RRAs are related to Type II action letters and are issued for urgent participant safety concerns that require change(s) in the protocol and/or consent form.

8.3.6 Changes to accrual status or study completion must be reported promptly to the CIRB. Whenever the CIRB determines that a change was not reported promptly or was not consistent with ensuring the participant's continued welfare, the CIRB will determine whether the implementation of the change without CIRB approval constituted serious noncompliance.

8.4 Study Memos

8.4.1 Study memos are memos, letters, emails, or broadcast emails that are distributed by the Study Chair, or other individual on the Study Chair's behalf to communicate study-specific information to various stakeholders in the study. There are two types of memo submissions:

8.4.1.1 Memos that do not impact study participants, and

8.4.1.2 Memos that potentially impact study participants or the conduct of the research.

8.4.2 If a Study Memo does not impact study participants, a CIRB Operations Office does not acknowledge the memo.

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8.4.3 If a Study Memo potentially impacts study participants or the conduct of the research, the memo is forwarded to the Chair, Vice Chair, or designee for review and a determination.

8.4.3.1 If the reviewer determines that the content of the memo may have a negative impact on study participants or represents more than a minor change to the conduct of the study, it is sent to the convened CIRB to review and to determine if any further action is required.

8.4.3.2 If the reviewer determines that the content of the memo has no impact, or a positive impact on study participants, the reviewer will issue an acknowledgment of the information on behalf of the CIRB and may consider whether study participants should be notified of the information if this is not already addressed in the memo.

8.5 Review of Editorial or Administrative Amendments

Editorial or administrative amendments are changes to protocol and consent forms that do not affect the study design, patient risk, or human subject protection and which are not considered changes in research. The CIRB Operations Office reviews and acknowledges editorial or administrative amendments on behalf of the CIRB after receipt of the change from the CTEP or DCP Protocol Information Office (PIO).

8.5.1 The following protocol changes are considered editorial or administrative amendments and qualify as editorial or administrative amendments for CIRB review:

8.5.1.1 Typographical correction, except if the change results in a change in patient risk (i.e. change eligibility from < to > XYZ; or change dose from mg to mcg).

8.5.1.2 Rephrasing a sentence or section to add clarity as long as the change does not affect the scientific intent, study design, patient risk, or human subject protection.

8.5.1.3 Reformatting the document as long as the change does not affect the scientific intent, study design, patient risk or human subject protection.

8.5.1.4 Address, telephone, or e-mail changes, except changes to the Principal Investigator or Protocol Chair contact information.

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- 8.5.1.5 Addition/deletion of physician co-investigators to studies that do not utilize a Pharmaceutical Management Branch-supplied agent.
- 8.5.1.6 Addition/deletion of non-physician co-investigators to any trial.
- 8.5.1.7 Addition/deletion of an institution to a CTEP U10 Cooperative Group ‘Groupwide’ study.
- 8.5.1.8 Standardization of protocol language inconsistencies, as long as the change does *not* affect the scientific intent, study design, patient risk, or human subject protection.
- 8.5.2 The following protocol changes are considered amendments and do **not** qualify as editorial or administrative amendments:
 - 8.5.2.1 Typographical correction that may affect patient safety (i.e., change eligibility from < to > XYZ; change dose from mg to mcg, or risk, regardless of whether risk is increased or decreased).
 - 8.5.2.2 Addition/deletion of an institution to a CTEP U10 Cooperative Group ‘limited institution’ study if the participants are individually named on the title page of the study.
 - 8.5.2.3 Addition/deletion of physician co-investigators to studies that utilize a Pharmaceutical Management Branch-supplied agent.
 - 8.5.2.4 Rephrasing a line or section that results in a change of scientific intent, study design, or affects human subject protection.
 - 8.5.2.5 Reformatting the document that results in a change of scientific intent, study design, or affects human subject protection.
 - 8.5.2.6 A change of Protocol Chair or Principal Investigator.
 - 8.5.2.7 A change of institution for the Principal Investigator or any physician co-investigator on a study with a Pharmaceutical Management Branch-supplied agent.
 - 8.5.2.8 The addition/deletion of a coordinating group to an intergroup study.
 - 8.5.2.9 A change in accrual targets.
- 8.5.3 CIRB Review of Editorial or Administrative Amendments

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8.5.3.1 Determination of Compliance

8.5.3.1.1 The CIRB Operations Office reviews the proposed changes and forwards the submission to the CIRB Administrator with a recommendation as to whether the submission meets the definition of an editorial or administrative amendment.

8.5.3.1.2 The CIRB Administrator determines whether the submission meets the definition of an editorial or administrative amendment.

- a. If the CIRB Administrator determines that the changes meet the definition of an editorial or administrative amendment the submission is acknowledged on behalf of the CIRB.
- b. If the CIRB Administrator determines that the changes do **not** meet the definition of editorial or administrative amendments the changes are forwarded for CIRB review as an amendment (change in research) per section 8.3.

8.6 Continuing Review

8.6.1 The CIRB conducts continuing review of all approved research activities in accordance with the requirements of 45 CFR 46.109(e) and, when applicable, 21 CFR 56.109(f).

8.6.2 Continuing review occurs as long as the research remains active for long-term follow-up of participants or until the requirements for closure of a study outlined in section 5.9.13 have been met. This includes when the research is permanently closed to enrollment of new participants and all participants have completed all research-related interventions and the remaining research activities are limited to the collection and/or analysis of identifiable information.

8.6.3 The CIRB conducts continuing review of research of approved studies at intervals appropriate to the degree of risk to which subjects are exposed. In no case is the interval between reviews longer than one calendar year

8.6.3.1 The CIRB conducts continuing review for all research under their purview. This is to ensure compliance with FDA regulations that still requires continuing review for research.

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- 8.6.4 During continuing review, the CIRB considers whether any significant new findings reported (i.e. findings included in a DSMB report or the continuing review application) might impact the participants’ willingness to continue participation. If the CIRB determines that the new findings do impact the participants’ willingness to continue, the CIRB will require that subjects be notified of the information.
 - 8.6.5 During continuing review, the CIRB evaluates whether recruitment materials, advertisements, or information to participants is sufficient and/or appropriate.
 - 8.6.6 Frequency of review required for a specific study is determined at initial and continuing review and is appropriate to the degree of risk.
 - 8.6.7 The approval period for continuing review begins when the CIRB provides final approval for the continuing review submission. The approval period is unaffected by amendment reviews.
 - 8.6.8 For continuing review, if the research does not receive approval to continue before the end of the current approval period, approval expires and all research activity must stop. In such circumstances, the CIRB may allow for continuation of the research for those participants already enrolled if it is determined to be in their best interests.
 - 8.6.9 The CIRB considers the rate of accrual and its impact on the feasibility of the study. Questions regarding the rate of accrual are directed to CTEP, which is responsible for monitoring trials for slow accrual.
 - 8.6.10 The CIRB has authority to determine which research activities need verification from sources other than the Study Chair that no material changes in the research have occurred since the previous CIRB review. Sources other than the Study Chair may include copies of OHRP Determination Letters, FDA audits information, “whistleblowers,” reports from any data monitoring committees established by the study, and CTEP/DCP.
- 8.7 Review of Recruitment Material and Advertisements
- 8.7.1 The CIRB will review the content of recruitment materials and advertisements, the mode of communication, and the final copy in accordance with the FDA Recruiting Study Subjects Information Sheet (dated 9/98) located at the following URL:
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm>.
Recruitment materials are considered documents directed to potential study participants.

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- 8.7.2 Recruitment materials and advertisements approved by the CIRB will not:
- 8.7.2.1 Include exculpatory language;
 - 8.7.2.2 State or imply a certainty of a favorable outcome or other benefits beyond what is outlined in the consent documentation and protocol;
 - 8.7.2.3 Make claims, either explicitly or implicitly, about an investigational drug, biologic, or device that are inconsistent with FDA labeling;
 - 8.7.2.4 Refer to an investigational drug, biologic, or device as a “new drug” or “new treatment” without explaining that the test article is investigational;
 - 8.7.2.5 Emphasize any payment to be made to subjects or allow compensation for participation in a study of an investigational drug or device to include a coupon for a discount on the purchase price of the product once it has been approved for marketing; and
 - 8.7.2.6 Promise “free treatment” when the intent is only to say participants will not be charged for taking part in the study.
- 8.7.3 Information included in recruitment materials and advertisements are limited to the information prospective study participants need to determine their eligibility and interest. The information that can be conveyed includes:
- 8.7.3.1 The name and address of the Researcher or research facility;
 - 8.7.3.2 The purpose of the research or the condition under study;
 - 8.7.3.3 In summary form, the criteria that will be used to determine eligibility for the study;
 - 8.7.3.4 A brief list of benefits to study participants, if any;
 - 8.7.3.5 The time or other commitment required of the study participants; and
 - 8.7.3.6 The location of the research and the person or office to contact for further information.

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- 8.7.4 Recruitment materials and advertisements submitted for CIRB review require a distribution plan. Submission of drafts of materials or scripts for videos prior to production is encouraged since changes required by the CIRB could be costly to make after production.
- 8.7.5 Approval for recruitment material requires the submission of the final copy.
- 8.8 Review of Materials Directed to Study Participants
 - 8.8.1 The CIRB reviews materials to be provided to study participants. Examples of these materials include letters directed to study participants and medication calendars or pill diaries.
- 8.9 Translated Documents
 - 8.9.1 The CIRB Operations Office (per section 5.9.9), CIRB Chair, Vice Chair, or designee verifies the following:
 - 8.9.1.1 The version date on all submitted documents matches with the most current CIRB-approved protocol;
 - 8.9.1.2 The study ID number and title match the most current CIRB-approved protocol; and
 - 8.9.1.3 The study ID number, title, and Protocol Version Date included on the Certificate of Accuracy match those on the submitted English language versions and correspond with the most current CIRB-approved protocol.
- 8.10 Review of CTEP Action Letters and Adverse Event Reports
 - 8.10.1 CTEP Action Letters
 - 8.10.1.1 CTEP Type I Action Letters require immediate suspension of accrual to the study. Upon receipt from CTEP, the CIRB Operations Office immediately forwards Type I Action Letters to the Chair for review and acknowledgment. The CIRB Operations Office posts the Action Letter and information pertaining to the suspension of accrual to the CIRB website.
 - 8.10.1.2 CTEP Type II Action Letters are issued by CTEP and sent to the Study Chair(s) accompanied by a Request for Rapid Amendment

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(RRA). The CIRB Operations Office is copied on the RRA and takes the following actions:

- 8.10.1.2.1 Identifies affected studies on the CIRB menu.
- 8.10.1.2.2 Forwards the RRA to the CIRB Chair, Vice Chair, or designee to determine if the anticipated amendment qualifies for expedited review as outlined in the OHRP Correspondence dated September 29, 2008 and located at the following URL:
<https://www.hhs.gov/ohrp/regulations-and-policy/guidance/september-29-2008-letter-to-jeffrey-abrams/index.html>.
 - a. If the changes do not qualify for expedited review, the CIRB Chair notifies CTEP and accrual to the study must be suspended until the consent form can be revised.

8.10.2 Adverse Event Reports

- 8.10.2.1 The CIRB does not review individual adverse event reports pertaining to studies when the study has a DSMB or sufficient monitoring plan. The CIRB reviews relevant data contained in current DSMB reports and study toxicity reports at the time of continuing review.
- 8.10.2.2 The CIRB Adverse Event Subcommittees review adverse event reports pertaining to studies that do not have a DSMB or sufficient monitoring plan.
- 8.10.2.3 The following process is followed for review of adverse events reports for studies that do not have a DSMB or sufficient monitoring plan:
 - 8.10.2.3.1 CIRB Adverse Event Subcommittee members review adverse event reports to determine whether the related study's consent form continues to satisfy the requirements for IRB approval by ensuring that reasonably foreseeable risks are appropriately described.
 - 8.10.2.3.2 The reviewer may request additional information to complete the review or may request a conference call with the CIRB Chair and/or other members of the CIRB Adverse Event Subcommittee.

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8.10.2.3.3 CIRB Adverse Event Subcommittee member review includes one of the following recommendations based on the adverse event and the current study documentation:

- a. No changes to consent form and/or protocol;
- b. Consent form requires clarification of existing risk;
- c. New risk identified not currently in consent form and/or protocol – request additional information; or
- d. More information is required because the AE report contains preliminary information and a determination cannot be made.

8.10.2.4 The convened CIRB is provided with a report listing all adverse events reviewed since the last CIRB meeting, when applicable, and the recommended actions to be taken by the CIRB. The recommendations are discussed and the convened CIRB votes to accept or modify the recommendations.

8.11 Local Context Review

Local context reviews are considered minor changes to previously approved research and are reviewed and approved under expedited review procedures by CIRB members who serve on the CIRB’s Local Context Subcommittees.

8.11.1 Annual Signatory Institution Worksheet

8.11.1.1 The submission of the Annual Signatory Institution Worksheet is provided to the CIRB Local Context Subcommittee member for review.

8.11.1.2 The review requires the review and approval of boilerplate language and other institutional requirements for the consent form. The CIRB Local Context Subcommittee member review for compliance with regulations.

8.11.1.3 The CIRB Local Context Subcommittee member may refer any review to the convened CIRB.

8.11.1.4 Signatory Institution Primary Contacts receive notification on an annual basis to review the Annual Signatory Institution Worksheet and submit any updates at that time.

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8.12 Annual Principal Investigator Worksheet

8.12.1 The submission of the Annual Principal Investigator Worksheet is provided to the CIRB Local Context Subcommittee member.

8.12.2 The CIRB Local Context Subcommittee member considers the resources available to the Principal Investigator to conduct research. Considerations include the following:

8.12.2.1 Adequate time for the Principal Investigator to conduct and complete the research;

8.12.2.2 Adequate number of qualified staff;

8.12.2.3 Adequate facilities;

8.12.2.4 Access to a population that will allow recruitment of the necessary number of participants within inclusion/exclusion criteria as defined by the protocol;

8.12.2.5 Availability of medical resources that participants may need as a consequence of the research.

8.12.3 The CIRB Local Context Subcommittee member considers the informed consent process as defined for the Principal Investigator and supporting research staff.

8.12.3.1 The CIRB Local Context Subcommittee member considers the safeguards in effect to ensure privacy and confidentiality.

8.12.3.2 The CIRB Local Context Subcommittee member reviews the considerations for vulnerable populations.

8.12.3.2.1 The use of legally authorized representatives, the plan to assess capacity, and the process for enrolling participants using a legally authorized representative. When a legally authorized representative is allowed, the legally authorized representative sign and date the consent form and is provided a copy of the signed consent form.

8.12.3.2.2 Safeguards are provided for any population being enrolled by the Principal Investigator, including:

- a. Children;
- b. Pregnant women and fetuses;
- c. Economically or educationally disadvantaged;
- d. Persons with impaired decision-making capacity;

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e. Physically impaired.

8.12.3.2.3 The Principal Investigator provides the Signatory Institution’s policy related to whether assent must be documented and the process to document assent.

8.12.3.3 The CIRB Local Context Subcommittee member assesses the conduct of the research as defined as:

8.12.3.3.1 Setting where research will be conducted;

8.12.3.3.2 Whether the population is vulnerable to coercion or undue influence and how this is minimized;

8.12.3.3.3 Participant recruitment and enrollment criteria;

8.12.3.3.4 Amount and timing of payments to participants and the potential influence of any payments.

8.12.3.3.5 Adequate time is provided to the participant or representative to review the consent form.

8.12.3.4 The CIRB Local Context Subcommittee member makes a determination about the local context considerations of the Principal Investigator.

8.12.3.5 The CIRB Local Context Subcommittee member may refer any review to the convened CIRB.

8.12.3.6 The Principal Investigator must submit a Study-Specific Worksheet for each study the Principal Investigator wants to open. The Study-Specific Worksheet confirms the Principal Investigator will conduct the study according to their approved Annual Principal Investigator Worksheet or documents what changes the Principal Investigator will make in the conduct of the study.

8.12.3.7 Principal Investigators and Signatory Institution Primary Contacts receive notification on an annual basis to review the Annual Principal Investigator Worksheet and submit any updates at that time.

8.13 Study-Specific Worksheet

8.13.1 Submitted Study-Specific Worksheets which include no changes to the information provided on the CIRB-approved Annual Principal Investigator Worksheet are considered approved by the CIRB upon verification by the CIRB Operations Office.

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8.13.2 Submitted Study-Specific Worksheets for which the only change to the information provided on the CIRB-approved Annual Principal Investigator Worksheet is the inclusion of translated copies of CIRB-approved documents are considered approved by the CIRB upon verification by the CIRB Operations Office Staff that there is no other deviation, and that the translated documents meet the requirements described in section 5.9.9 and 8.9 of this SOP.

8.13.3 Submitted Study-Specific Worksheets which deviate from considerations described in the CIRB-approved Annual Principal Investigator Worksheet are provided to the CIRB Local Context Subcommittee member for a final determination.

8.13.3.1 The CIRB Local Context Subcommittee member reviews the submission and takes into consideration any changes from the Annual Principal Investigator Worksheet related to the specific study to be opened with the CIRB.

8.13.3.2 The CIRB Local Context Subcommittee member may refer any review to the convened CIRB.

8.14 Potential Unanticipated Problems and/or Serious or Continuing Noncompliance Reporting Worksheet

8.14.1 The CIRB Local Context Subcommittee member is provided the Potential Unanticipated Problem and/or Serious or Continuing Noncompliance Reporting Worksheet and the management plan for review and to make a determination of whether the incident, experience, or outcome is an unanticipated problem and/or serious or continuing noncompliance.

8.14.1.1 To make a determination that an incident, experience or outcome is an unanticipated problem, ALL of the following criteria must be met:

8.14.1.1.1 The incident, experience, or outcome is unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol or the investigator’s brochure and the characteristics of the subject population being studied;

8.14.1.1.2 There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and

8.14.1.1.3 Subjects or others are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or

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recognized due to the incident, experience, or outcome.

8.14.1.2 To make a determination that an incident, experience, or outcome is serious or continuing noncompliance, the following definitions must be met:

8.14.1.2.1 Noncompliance is a failure to meet the requirements of the applicable Federal regulations and/or the requirements of the CIRB.

8.14.1.2.2 Serious noncompliance is noncompliance that adversely affects the rights and welfare of study participants.

8.14.1.2.3 *Continuing* noncompliance is a systematic and habitual disregard of the requirements or decisions of the CIRB or of Federal regulations. Continuing noncompliance is an indication of a pattern that, if unaddressed, could jeopardize the rights and welfare of research participants or the integrity of the study data due to noncompliance with the protocol, Federal regulations, and/or the requirements of the CIRB.

8.14.1.3 The CIRB Local Context Subcommittee member may refer any review to the convened CIRB.

8.15 Locally-Developed Material Submission

8.15.1 The CIRB Local Context Subcommittee member is provided the locally developed material directed to study participants and any supporting documents for review via the Annual Signatory Institution Worksheet or the Study-Specific Worksheet.

8.15.2 The CIRB Local Context Subcommittee member makes a determination regarding the locally-developed material.

8.15.3 Any recruitment material or advertisements must be determined to comply with the requirements defined in Section 8.7.

8.15.4 The CIRB Local Context Subcommittee member may refer any review to the convened CIRB.

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Section 9.0 Research Requiring an IND or IDE

9.1 Review of Research Requiring an IND

9.1.1 When research involves the use of a drug other than the use of a marketed drug in the course of medical practice:

9.1.1.1 The drug has an IND; or

9.1.1.2 The study meets one of the FDA exemptions from the requirement to have an IND.

9.1.1.3 Exemption 1

9.1.1.3.1 The drug product is lawfully marketed in the United States.

9.1.1.3.2 The study is not intended to support FDA approval of a new indication or a significant change in the product labeling.

9.1.1.3.3 The study is not intended to support a significant change in the advertising for the product.

9.1.1.3.4 The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

9.1.1.3.5 The study is conducted in compliance with IRB and informed consent regulations set forth in parts 21 CFR 50 and 21 CFR 56.

9.1.1.3.6 The study is conducted in compliance with 21 CFR 312.7 (promotion and charging for investigational drugs).

9.1.1.4 Exemption 2

9.1.1.4.1 A clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:

- Blood grouping serum.
- Reagent red blood cells.
- Anti-human globulin.

9.1.1.4.2 The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis

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made by another, medically established, diagnostic product or procedure.

9.1.1.4.3 The diagnostic test is shipped in compliance with 21 CFR 312.160.

9.1.1.5 Exemption 5

9.1.1.5.1 A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

9.1.2 If the Study Chair does not already have an IND, the Study Chair is queried regarding the intent to obtain an IND or justification for not submitting the study to the FDA.

9.1.3 When determining if an IND is required, the CIRB considers the FDA Guidance for Industry IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer located at the following URL:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071717.pdf>.

9.1.4 If there is disagreement regarding the need for an IND, the CIRB will require that the Study Chair or sponsor contact the FDA to obtain written documentation that an IND is not necessary.

9.1.5 When an IND is required to conduct the research, the CIRB provides timely review and approval of research. However, the Study Chair must submit verification of the IND before the study is open to accrual.

9.2 Review of Research Involving Medical Devices

9.2.1 Before reviewing research involving an unapproved medical device for human use or an approved medical device that is being used in a manner outside of the approved label, the CIRB will determine if the device is a Significant Risk (SR) Device, a Non-Significant Risk (NSR) Device, or whether the research use of the device is exempt from the Investigational Device Exemption (IDE) regulations.

9.2.1.1 If the CIRB determines that the device is NSR, this finding will be included in the minutes, and the CIRB may proceed to review the research activities and investigator under its normal procedures for reviewing research projects.

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9.2.1.2 If the FDA has issued an IDE for the proposed use of the device, then it is automatically an SR device. This finding will be noted in the minutes.

9.2.1.3 If FDA has not issued an IDE for the proposed use of the device, then the CIRB shall determine whether the device is a SR device using the following definition:

A significant risk device means an investigational device that meets any of the following criteria (FDA 21 CFR 812.3(m)):

9.2.1.3.1 It is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.

9.2.1.3.2 It is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.

9.2.1.3.3 It is for a use of substantial importance in diagnosis, 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

9.2.1.3.4 Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Note: If the subject must undergo a medical procedure as a part of the study, and that medical procedure is not one that the subject would otherwise undergo as part of standard medical care, the CIRB must consider the risks associated with the procedure as well as the use of the device. If potential harm to subjects could be life-threatening, could result in permanent impairment of body function, or permanent damage to body structure, the device should be considered SR.

9.2.1.4 If the CIRB determines the device is SR, and there is no IDE assigned, it will provide the coordinating group with its finding. The Group is responsible for notifying the FDA of the CIRB's SR determination. The CIRB will not approve the research until the Group provides proof that the FDA has granted an IDE. In most instances, the proof will be a copy of the FDA letter granting the IDE. However, if the FDA has not responded to the IDE application, as described in FDA 21 CFR 812.30, this proof may consist of a letter showing that an IDE application was

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submitted at least 30 days prior to the date on which the CIRB reviews the research.

9.2.1.5 If the CIRB determines that the investigation meets one of the IDE exemptions listed at 21 CFR 812.2(c), this finding will be noted in the minutes, and the CIRB will not make an SR/NSR determination. Also, if the investigation involves a device that is cleared for marketing through the PMA process, and the device is being studied for the purpose(s) for which the device is labeled, the CIRB will consider the investigation exempt from the IDE regulations. This finding is noted in the minutes, and the CIRB will not make an SR/NSR determination.

9.2.1.6 If the research is being conducted to determine the safety and effectiveness of a device, the device fulfills the requirements for an abbreviated IDE if all of the following are met:

9.2.1.6.1 The device is not a banned device.

9.2.1.6.2 The sponsor labels the device in accordance with 21 CFR 812.5.

9.2.1.6.3 The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval.

9.2.1.6.4 The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation is waived.

9.2.1.6.5 The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations.

9.2.1.6.6 The sponsor maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21 CFR 812.150(b) (1) through (3) and (5) through (10).

9.2.1.6.7 The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7).

9.2.1.6.8 The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

9.2.1.7 If the research is being conducted to determine the safety and effectiveness of a device, the device qualifies for an IDE

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exemption if it fulfills the requirements of one of the following categories:

- 9.2.1.7.1 A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
- 9.2.1.7.2 A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
- 9.2.1.7.3 A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
 - a. Is noninvasive.
 - b. Does not require an invasive sampling procedure that presents significant risk.
 - c. Does not by design or intention introduce energy into a participant.
 - d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- 9.2.1.7.4 A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put participants at risk.
- 9.2.1.7.5 A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

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Section 10.0 Unanticipated Problems and Serious or Continuing Noncompliance

10.1 Overview

Federal regulations (45 CFR 46.103(a) and (b)(5) under pre-2018 Requirements, 45 CFR 46.108(a)(4) under 2018 Requirements, and 21 CFR 56.108(b)(1-3) for FDA-regulated studies) require prompt reporting to the CIRB, appropriate institutional officials, and agency heads (OHRP, and when involving a regulated product, the FDA) of:

- any unanticipated problems involving risks to human subjects or others;
- any serious noncompliance with the regulations or the requirements or determinations of the CIRB;
- any continuing noncompliance with the regulations or the requirements or determinations of the CIRB;
- suspension or termination of CIRB approval.

10.2 Unanticipated Problems

10.2.1 Definition

10.2.1.1 Unanticipated problems warrant consideration of substantive changes in the research protocol or consent form or other corrective actions to protect the safety, welfare, or rights of subjects or others. Unanticipated problems include any incident, experience, or outcome that meets **ALL** the following criteria:

- 10.2.1.1.1 The incident, experience, or outcome is unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol or the investigator’s brochure and the characteristics of the subject population being studied;
- 10.2.1.1.2 There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and
- 10.2.1.1.3 Subjects or others are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized due to the incident, experience, or outcome.

10.2.2 Categories of Unanticipated Problems

10.2.2.1 Local unanticipated problems occur at and are limited to a specific institution. Signatory Institutions participating in the

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CIRB provide a report of the local unanticipated problems with a management plan to the CIRB for review. The CIRB reports to OHRP, CTEP, DCP, the local institution and, when applicable, FDA.

10.2.2.2 Trial-wide unanticipated problems, impacting the overall research occur at or are identified by the NCI-supported coordinating groups or CTEP. These are submitted to and reviewed by the CIRB and reported to OHRP, CTEP, DCP, and when applicable, FDA.

10.2.3 Local Unanticipated Problems

10.2.3.1 Local unanticipated problems are problems that occur at an institution and do not impact the trial nationally. The principal investigator, local IRB, and institution typically become aware of the event directly from the subject or from information received about a subject or research activity.

10.2.3.2 The Signatory Institution Principal Investigator reports the event to the CIRB if the Signatory Institution Principal Investigator determines that an event potentially meets the definition of an unanticipated problem. The CIRB Local Context Subcommittee determines if the incident, experience, or outcome constitutes an unanticipated problem. If so, the CIRB reports the unanticipated problem to OHRP, CTEP, DCP, the local institution and, when applicable, FDA.

10.2.3.3 The Signatory Institution Principal Investigator is required to report serious adverse events and protocol deviations to the coordinating group, per the Group’s guidelines. These events are not reported to the CIRB unless the Principal Investigator believes they represent a potential unanticipated problem per the definition included in section 10.2.1.1 of these SOPs.

10.2.4 Trial-Wide Unanticipated Problems Impacting the Overall Research

10.2.4.1 Unanticipated problems, impacting the overall research, are incidents, experiences, or outcomes which meet the regulatory definition in section 10.2.1.1 of these SOPs and impact the trial across all or most sites. Possible unanticipated problems are typically identified by the Study Chair or coordinating group who are responsible for notifying the CIRB Operations Office. Potential unanticipated problems may also be identified by CTEP, DCP or the CIRB. The CIRB is responsible for

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determining if the incident, experience, or outcome constitutes an unanticipated problem and if so, will report the unanticipated problem to OHRP, CTEP, DCP and, when applicable, FDA.

10.2.5 Reporting Unanticipated Problems to the CIRB

10.2.5.1 Potential unanticipated problems require prompt reporting to the CIRB as these problems potentially place subjects or others at greater risk of physical or psychological harm than was previously recognized and warrant consideration of substantive changes in the protocol or informed consent process/document or other action to protect the safety, welfare, or rights of subjects. Reporting must occur for all studies under the CIRB, including those that have been suspended or terminated by the CIRB.

10.2.5.2 The CIRB is notified of a *locally-occurring* unexpected incident, experience, or outcome via the following mechanisms:

10.2.5.2.1 The Signatory Institution Principal Investigator notifies the CIRB Operations Office within seven (7) days of its receipt of the information related to serious adverse events that appears to meet the criteria of an unanticipated problem.

10.2.5.2.2 The Signatory Institution Principal Investigator notifies the CIRB Operations Office within fourteen (14) days of its receipt of information related to other potential unanticipated problems.

10.2.5.3 The CIRB is notified of a *trial-wide* unexpected incident, experience, or outcome via the following mechanisms:

10.2.5.3.1 The Study Chair notifies the CIRB Operations Office of trial-wide unexpected incidents, experiences, or outcomes in a timely manner. CTEP or DCP may assist the Study Chair in notifying the CIRB.

10.2.5.3.2 If the incident, experience, or outcome involves an investigational device, the Study Chair will report to the CIRB the results of its evaluation of any unanticipated adverse device effect within ten (10) working days after receiving notice of the effect. [21 CFR 812.46(b) and 21 CFR 812.150(b)(1)].

10.2.6 CIRB Determination of a Local Unanticipated Problem

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10.2.6.1 When the CIRB Operations Office receives information regarding a local incident, experience, or outcome potentially meeting the definition of an unanticipated problem, CIRB Operations Office forwards the report and management plan to a CIRB Local Context Subcommittee member for review.

10.2.6.2 Review

10.2.6.2.1 The CIRB Local Context Subcommittee member reviews the report and management plan and determines if the incidence, experience, or outcome meets the criteria of an unanticipated problem.

10.2.6.2.2 Any submission that the CIRB Local Context Subcommittee member determines is an unanticipated problem is reported as required in Section 10.5.

10.2.6.2.3 If the CIRB Local Context Subcommittee member determines that the potential unanticipated problem requires review by the convened CIRB, it is either placed on the next scheduled meeting agenda or an ad hoc meeting is convened based on the recommendation of the CIRB Local Context Subcommittee member and the Chair and/or Vice Chair. The recommendation of the reviewer will be considered during the CIRB’s deliberations regarding the report.

10.2.6.3 If a conference call with the Signatory Institution Principal Investigator or Signatory Institution representative(s) is required to obtain any additional information prior to the CIRB’s determination, a conference call will be scheduled by the CIRB Operations Office. If the review of the potential unanticipated problem occurs during a convened CIRB meeting, the Signatory Institution Principal Investigator or Signatory Institution representative(s) will be invited to attend the meeting to address any questions that arise.

10.2.6.4 These policies and procedures, relevant regulations (45 CFR 46.103(b)(5) under pre-2018 Requirement, 45 CFR 46.108(a)(4) under 2018 Requirements, and 21 CFR 56.108(b)(1) for FDA-regulated studies), copies of appropriate guidance, and the submitted report are made available to the CIRB Local Context Subcommittee members for reference and to all CIRB members for discussion, if required.

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10.2.6.5 If the review is conducted by the convened CIRB, during the meeting the CIRB determines whether the incident, experience, or outcome meets the criteria of an unanticipated problem as described in these SOPs.

10.2.7 CIRB Determination of a Trial-Wide Unanticipated Problem

10.2.7.1 When the CIRB Operations Office receives information regarding a trial-wide incident, experience, or outcome potentially meeting the definition of an unanticipated problem, CIRB Operations Office forwards the information or report to the CIRB Chair, Vice Chair, or designee for a preliminary review.

10.2.7.2 Preliminary Review

10.2.7.2.1 The Chair, Vice Chair, or designee determines whether the CIRB needs to address the report immediately based on participant safety. If the Chair, Vice Chair, or designee determines that the reported occurrence does not impact the safety of subjects or others, the event is not an unanticipated problem. If the Chair, Vice Chair, or designee determines that the reported occurrence does impact the safety of subjects or others then the report is forwarded for review by the convened CIRB. If the next regularly scheduled meeting is within seven (7) working days, the Chair, Vice Chair, or designee may have the occurrence added to the agenda for that meeting. The Chair, Vice Chair, or designee may request an ad hoc meeting be convened to review the report if warranted based on safety concerns.

10.2.7.2.2 If the reported incident, experience, or outcome impacts the safety of subjects or others, the Chair, Vice Chair, or designee reviews the report and formulates a recommendation to be forwarded to the convened CIRB. Alternatively, the Chair, Vice Chair, or designee may assign the preliminary review to a CIRB member who will present their review during the convened CIRB meeting. The recommendation of the reviewer will be considered during the CIRB's deliberations regarding the report.

10.2.7.3 If a conference call with the Study Chair, coordinating group, and CTEP or DCP is required to obtain any additional information prior to the CIRB's determination, a conference call

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will be scheduled by the CIRB Operations Office. If a conference call cannot be scheduled during the CIRB meeting, the CIRB Chair has the option to conference with the Study Chair, coordinating group, and CTEP or DCP prior to the CIRB meeting.

10.2.7.4 These policies and procedures, relevant regulations (45 CFR 46.103(b)(5) under pre-2018 Requirements, 45 CFR 46.108(a)(4) under 2018 Requirements, and 21 CFR 56.108(b)(1) for FDA-regulated studies), copies of appropriate guidance, and the submitted report are made available to CIRB members for discussion.

10.2.7.5 During its review, the CIRB determines whether the incident, experience, or outcome meets the criteria for an unanticipated problem as described in these SOPs.

10.3 Serious or Continuing Noncompliance

10.3.1 Definitions

10.3.1.1 Noncompliance is a failure to meet the requirements of the applicable Federal regulations and/or the requirements of the CIRB.

10.3.1.2 *Serious* noncompliance is noncompliance that adversely affects the rights and welfare of study participants or results in any untoward medical occurrence that meets the criteria of “serious” or significantly impacts the integrity of study data. Serious is defined as side effects that may require hospitalization or may be irreversible, long-term, life-threatening, or fatal. The CIRB may also consider as serious those events which, based on appropriate medical judgment, may jeopardize the patient or subject and am require medical or surgical intervention to prevent one of the outcomes above.

10.3.1.3 *Continuing* noncompliance is a systematic and habitual disregard of the requirements or decisions of the CIRB or of Federal regulations. Continuing noncompliance is an indication of a pattern that, if unaddressed, could jeopardize the rights and welfare of research participants or the integrity of the study data due to noncompliance with the protocol, Federal regulations, and/or the requirements of the CIRB.

10.3.2 Categories of Noncompliance

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10.3.2.1 Local noncompliance occurs at and is limited to a specific institution. The Signatory Institution is responsible for reporting local potential serious and/or continuing noncompliance to the CIRB.

10.3.2.2 Trial-wide noncompliance, impacting the overall research, occurs at or is identified by the CIRB Chair, CIRB Operations Office, NCI-supported coordinating groups, CTEP, DCP or others involved in the research. Reports of trial-wide noncompliance are submitted to and reviewed by the CIRB and reported to OHRP, CTEP, DCP and, when applicable, FDA.

10.3.3 Local Noncompliance

10.3.3.1 Local noncompliance is noncompliance that occurs at an institution and does not impact the trial nationally. Local potential serious and/or continuing noncompliance must be reviewed by the CIRB Local Context Subcommittee member on behalf of the CIRB according to these policies and procedures. If the CIRB determines that there is serious or continuing noncompliance, the CIRB has the responsibility to comply with the regulations and guidance and report the event to OHRP, CTEP, DCP, the Signatory Institution, and, when applicable, FDA.

10.3.3.2 Local noncompliance may include complaints, protocol deviations, and audit findings.

10.3.4 Trial-Wide Noncompliance

10.3.4.1 Trial-wide noncompliance is noncompliance on the part of the CIRB, the Study Chair, or coordinating group and impacts the trial across all or most participating institutions. The CIRB is responsible for making a determination regarding serious or continuing noncompliance and for reporting the noncompliance to OHRP, CTEP, DCP, and, when applicable, FDA.

10.3.5 Reporting Local and Trial-wide Potential Serious and/or Continuing Noncompliance to the CIRB

10.3.5.1 Local and trial-wide potential serious and/or continuing noncompliance requires prompt reporting to the CIRB to determine if the potential serious and/or continuing noncompliance requires immediate action to protect the safety,

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welfare, or rights of research participants. Reporting must occur for all studies under the CIRB, including those that have been suspended or terminated by the CIRB.

10.3.5.2 All reports of potential serious and/or continuing noncompliance are reviewed by the CIRB. A management plan is required to be submitted with all reports of potential serious and/or continuing noncompliance.

10.3.5.3 Possible serious and/or continuing noncompliance may be identified by the CIRB Chair, the CIRB Operations Office, CTEP, DCP, others involved in the research, those at Signatory Institutions and their Component, and Affiliate Institutions, or those in the local research community.

10.3.6 CIRB Determination of Local Serious or Continuing Noncompliance

10.3.6.1 When the CIRB Operations Office receives information regarding local potential serious and/or continuing noncompliance, the CIRB Operations Office forwards the report and management plan to the CIRB Local Context Subcommittee member for review.

10.3.6.2 Review

10.3.6.2.1 The CIRB Local Context Subcommittee member reviews the report and management plan and determines if the incident, experience, or outcome meets the CIRB’s definition of serious or continuing noncompliance.

10.3.6.2.2 Any submission that the CIRB Local Context Subcommittee member determines is serious or continuing noncompliance is reported as required in Section 10.5.

10.3.6.2.3 If the CIRB Local Context Subcommittee member determines that the potential serious or continuing noncompliance requires review by the convened CIRB, it is either placed on the next scheduled meeting agenda or an ad hoc meeting is convened based on the recommendation of the CIRB Local Context Subcommittee member and the Chair and/or Vice Chair. The recommendation of the reviewer will be considered during the CIRB’s deliberations regarding the report.

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10.3.6.3 If a conference call with the Signatory Institution Principal Investigator or Signatory Institution representative(s) is required to obtain any additional information prior to the CIRB’s determination, a conference call will be scheduled by the CIRB Operations Office. If the review of the potential serious and/or continuing noncompliance occurs during a convened CIRB meeting, the Signatory Institution Principal Investigator or Signatory Institution representative(s) will be invited to attend the meeting to address any questions that arise.

10.3.6.4 These policies and procedures, relevant regulations, copies of appropriate guidance, and the submitted report are made available to the CIRB Local Context Subcommittee members for reference and to all CIRB members for discussion, if required.

10.3.6.5 If the review is conducted by the convened CIRB, during the meeting the CIRB determines whether the incident, experience, or outcome meets the criteria of serious and/or continuing noncompliance as described in these SOPs.

10.3.7 CIRB Determination of Trial-Wide Serious or Continuing Noncompliance

10.3.7.1 When the CIRB Operations Office receives information regarding potential serious and/or continuing noncompliance, the CIRB Operations Office forwards the information or report to the CIRB Chair, Vice Chair, or designee for a preliminary review.

10.3.7.2 Preliminary Review

10.3.7.2.1 The CIRB Chair, Vice Chair, or designee determines whether the CIRB needs to address the report immediately based on participant safety. The CIRB Chair, Vice Chair, or designee may determine the report does not constitute noncompliance. If the CIRB Chair, Vice Chair, or designee determines that the report constitutes potential serious and/or continuing noncompliance, the report is forwarded for review by the convened CIRB. If the next regularly scheduled meeting is within seven (7) working days, the Chair, Vice Chair, or designee may have the occurrence added to the agenda for that meeting. The Chair, Vice Chair, or designee may request an ad hoc meeting be convened to review the report if warranted based on safety concerns.

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10.3.7.2.2 The CIRB Chair, Vice Chair, or designee reviews the report and formulates a recommendation to be forwarded to the convened CIRB. Alternatively, the Chair, Vice Chair, or designee may assign the preliminary review to a CIRB member who will present their review during the convened CIRB meeting. The recommendation of the reviewer will be considered during the CIRB’s deliberations regarding the report.

10.3.7.3 If a conference call with the Study Chair, coordinating group, and CTEP or DCP is required to obtain any additional information prior to the CIRB’s determination, a conference call will be scheduled by the CIRB Operations Office. If a conference call cannot be scheduled during the CIRB meeting, the CIRB Chair has the option to conference with the Study Chair, coordinating group, and CTEP or DCP prior to the CIRB meeting.

10.3.7.4 These policies and procedures, relevant regulations, guidance, and any documents related to the allegations will be made available to CIRB members for discussion.

10.3.7.5 During its review, the CIRB determines whether the information meets the definition of serious or continuing noncompliance as described in these SOPs.

10.4 Resolution of Locally-Occurring Unanticipated Problems and/or Serious or Continuing Noncompliance

10.4.1 The CIRB Local Context Subcommittee member determines an appropriate action in response to an unanticipated problem or a finding of serious and/or continuing noncompliance. The action depends upon the nature of the unanticipated problem or serious and/or continuing noncompliance and the effect on the rights, safety, and welfare of subjects. Possible actions to be taken by the CIRB Local Context Subcommittee member include but are not limited to:

10.4.1.1 Acceptance of the management plan;

10.4.1.2 Monitoring of the research or monitoring of the consent process at the Signatory Institution and its Component or Affiliate Institutions, as appropriate; or

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10.4.1.3 Defer to the convened CIRB to take further actions as defined in section 10.5.1.

10.4.2 If the CIRB Local Context Subcommittee member finds that substantive changes are required to either the protocol or consent form, the review will be deferred to the convened CIRB.

10.4.2.1 Whenever the CIRB Local Context Subcommittee member determines that the reported incident, experience, or outcome constitutes an unanticipated problem or serious and/or continuing noncompliance, the CIRB will notify OHRP and, when applicable, FDA.

10.4.2.2 The Signatory Official for the NCI CIRB and associated Human Research Protection Program is copied on all correspondence sent to OHRP and FDA.

10.5 Resolution of Trial-Wide Unanticipated Problems and/or Serious or Continuing Noncompliance

10.5.1 The CIRB determines an appropriate action in response to an unanticipated problem or a finding of serious and/or continuing noncompliance. The action depends upon the nature of the unanticipated problem or serious and/or continuing noncompliance and the effect on the rights, safety, and welfare of subjects. Possible actions include but are not limited to:

10.5.1.1 Suspension of the research;

10.5.1.2 Termination of the research;

10.5.1.3 Notification of current or past participants if such information will relate to the participants' willingness to continue to take part in the research;

10.5.1.4 Modification of the protocol and/or consent form;

10.5.1.5 Requiring current participants to re consent to participation;

10.5.1.6 Modification of the continuing review schedule;

10.5.1.7 Monitoring of the research or monitoring of the consent process;
or

10.5.1.8 Referral to other organizational entities, as required.

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10.5.2 If the CIRB finds that substantive changes are required to either the protocol or consent form:

10.5.2.1 The CIRB will determine whether research continues to satisfy the requirements for IRB approval under Federal regulation 45 CFR 46.111 and, when applicable, 21 CFR 56.111. If the CIRB determines that the requirements are no longer met, the CIRB must suspend accrual, suspend study activity, or suspend approval until it determines the study is safe to continue. The CIRB may also terminate the study.

10.5.2.2 The CIRB discusses with the Study Chair whether and how to notify participants of the substantive changes that could affect the participant’s willingness to continue participation. Past participants are considered in this discussion.

10.5.2.3 The CIRB notifies the Study Chair and coordinating group within twenty-one (21) days of its determination of an unanticipated problem or serious and/or continuing noncompliance and requests that the Study Chair/coordinating group submit a plan to address the problem within ten (10) working days. The CIRB may request that specific changes to the protocol, consent form, or other documentation be included in the plan.

10.5.2.4 Whenever the CIRB determines that the reported incident constitutes an unanticipated problem or serious and/or continuing noncompliance, the CIRB will notify OHRP and, when applicable, FDA. The Signatory Official for the NCI CIRB and associated Human Research Protection Program is copied on all correspondence sent to OHRP and FDA.

10.6 Reporting of an Unanticipated Problem or Serious and/or Continuing Noncompliance to Regulatory Agencies

10.6.1 If the CIRB determines that an incident, experience, or outcome constitutes an unanticipated problem or serious and/or continuing noncompliance, the CIRB Chair will notify OHRP and, when applicable, FDA per Federal regulations. The review outcome letter will be sent within fifteen (15) working days of the determination. The review outcome letter includes the Study Chair/coordinating group’s plan to address the unanticipated problem or serious and/or continuing noncompliance. If a plan of corrective action is not available at the time of the notification, then a preliminary outcome letter will be sent to OHRP

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and, when applicable, FDA. When the CIRB receives the Study Chair/coordinating group’s plan, a final outcome letter is sent to the regulatory agencies. The Signatory Official for the NCI CIRB and associated Human Research Protection Program is copied on all correspondence sent to OHRP and FDA.

10.6.2 When a trial-wide unanticipated problem or serious and/or continuing noncompliance are reported to regulatory agencies, the submission includes at a minimum, the following information:

10.6.2.1 Coordinating group;

10.6.2.2 Study number;

10.6.2.3 Study title;

10.6.2.4 A detailed description of the unanticipated problem or serious and/or continuing noncompliance;

10.6.2.5 A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem or serious and/or continuing noncompliance.

10.6.3 When a local unanticipated problem or serious and/or continuing noncompliance are reported to regulatory agencies, the submission includes at a minimum, the following information:

10.6.3.1 Signatory Institution;

10.6.3.2 Signatory Institution Principal Investigator or Signatory Institution Primary Contact;

10.6.3.3 Study number;

10.6.3.4 Study title;

10.6.3.5 A detailed description of the unanticipated problem and/or serious or continuing noncompliance;

10.6.3.6 A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem and/or serious or continuing noncompliance.

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10.6.4 Within two (2) working days of sending the CIRB’s review outcome letter to OHRP and FDA of a trial-wide unanticipated problem or serious and/or continuing noncompliance, the CIRB notifies local institutions for which the CIRB is the IRB of record that an unanticipated problem or serious and/or continuing noncompliance on a protocol has been reported to OHRP and FDA. This notification occurs via posting to the study-specific secure website.

10.6.5 Within two (2) working days of sending the CIRB’s review outcome letter to OHRP and FDA of a local unanticipated problem or serious and/or continuing noncompliance, the CIRB notifies the Signatory Institution for which the CIRB is the IRB of record that an unanticipated problem or serious and/or continuing noncompliance on a protocol has been reported to OHRP and FDA.

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Section 11.0 Retention of Records

11.1 Federal Guidelines for the Retention of Records

11.1.1 Per 45 CFR 46.115 and 21 CFR 56.115, the CIRB Operations Office maintains the following records electronically:

- 11.1.1.1 Copies of research protocols reviewed;
- 11.1.1.2 CTEP or DCP Consensus Review (scientific evaluation), when applicable;
- 11.1.1.3 Approved consent forms/parental permission forms;
- 11.1.1.4 Recruitment materials;
- 11.1.1.5 Applications for initial review, amendment review, continuing review;
- 11.1.1.6 Study progress reports or toxicity summaries, when applicable;
- 11.1.1.7 DSMB reports, when applicable;
- 11.1.1.8 Reports of unanticipated problems;
- 11.1.1.9 Reports of serious or continuing noncompliance;
- 11.1.1.10 Adverse event reports reviewed by the CIRB’s Adverse Event Subcommittee, when applicable;
- 11.1.1.11 Minutes of CIRB meetings;
- 11.1.1.12 Reviewer Findings;
- 11.1.1.13 Continuing review documents/reports;
- 11.1.1.14 Copies of all correspondence between the CIRB and the Study Chair, including study-specific memos;
- 11.1.1.15 CIRB member information as described in section 4.3.9;
- 11.1.1.16 Statements of significant new findings provided to subjects as required by 45 CFR 46.116(b)(5) under pre-2018

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Requirements, 45 CFR 46.116(c)(5) under 2018 Requirements, and 21 CFR 50.25(b)(5) for FDA-regulated studies.

- 11.1.1.17 Worksheets for the submission of local context considerations to the CIRB;
- 11.1.1.18 Correspondence related to local context consideration review;
- 11.1.1.19 Reviews conducted of local context Worksheets;
- 11.1.1.20 Investigator Brochure, when applicable;
- 11.1.1.21 Modifications to previously approved research;
- 11.1.1.22 Documentation related to CIRB exempt determinations;
- 11.1.1.23 Documentation for the rationale for conducting continuing review of research that would otherwise not require continuing review (per 45 CFR 46.109(f) (applicable under 2018 Requirements only));
- 11.1.1.24 Documentation of the rationale for an expedited reviewer’s determination that research appearing on the expedited review list is more than minimal risk (applicable for 2018 Requirements only).

11.2 Location of CIRB Records

- 11.2.1 CIRB records are electronically maintained on a network with access limited only to internal CIRB Operations Office staff with nightly off-site back-ups.
- 11.2.2 CIRB records shall be accessible for inspection and copying by authorized representatives of NCI, FDA, the OHRP, or other agencies, when appropriate jurisdiction exists, at reasonable times, and in a reasonable manner.

11.3 Length of Storage of CIRB Records

- 11.3.1 All records are stored for at least three (3) years after completion of the research, or longer if required by the study sponsor.
- 11.3.2 If a study is completed without participant enrollment, CIRB records are maintained for at least three years after completion.

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Section 12.0 Management and Revision of SOPs

12.1 Management

12.1.1 CIRB Operations Office maintains the CIRB Standard Operating Procedures.

12.1.2 The CIRB Operations Office maintains documentation of all changes to the CIRB SOPs. Old versions are retained for historical completeness.

12.1.3 An effective date appears on each page of the written policies and procedures. This date reflects the date when the policy version is activated.

12.1.4 The CIRB Initiative has a standing SOP Committee responsible for annual review and revision of the CIRB SOPs as needed as well as creation of new CIRB SOPs. The committee is comprised at a minimum of the following:

12.1.4.1 CIRB Administrator

12.1.4.2 Accreditation Lead

12.1.4.3. Additional staff of the CIRB Operations Office as needed

12.2 Creation and Revision of CIRB SOPs

12.2.1 Creation of a new SOP or revision of an existing SOP may be proposed in the course of the year.

12.2.2 The SOP Committee meets to discuss the need for revision or creation of a new SOP and considers the following:

12.2.2.1 Whether the current CIRB SOPs already address the matter appropriately,

12.2.2.2 Whether a revision to the current CIRB SOPs would be sufficient to address the matter, or

12.2.2.3 Whether a new CIRB SOP is required.

12.2.3 If the SOP Committee determines that a new or updated SOP is required:

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- 12.2.3.1 The SOP Committee may request input from other entities including CIRB Members, OHRP, FDA, CTEP, Cooperative Group, and other stakeholders as necessary.
- 12.2.3.2 A draft is provided to the Head of the CIRB Initiative and the NCI Project Officer/Contractive Office Representative (COR) and a timeline is established for completion and implementation.
- 12.2.3.3 When a specific SOP is updated, the update is made at the section level.
- 12.2.3.4 The SOP Committee determines an effective date for the new SOP.
- 12.2.3.5 The SOP Committee determines an appropriate plan for notification of stakeholders according to the CIRB SOP.

12.3 Annual Review of CIRB SOPs

- 12.3.1 The CIRB Standard Operating Procedures are reviewed annually for compliance with Federal regulations and applicable guidance and current procedures.
- 12.3.2 Annual review is conducted by the SOP Committee.
- 12.3.3 Annual review may result in a new or updated SOP.

12.4 Stakeholder Notification of Changes to CIRB SOPs

- 12.4.1 Changes in the CIRB SOPs may require notification of the appropriate stakeholders in the CIRB Initiative. These stakeholders include, but are not limited to:
 - 12.4.1.1 Adult and Pediatric CIRB Members
 - 12.4.1.2 CTEP and DCP including all components of the HRPP
 - 12.4.1.3 Study Chairs and coordinating groups
 - 12.4.1.4 Enrolled institutions, local IRBs, and local research staff
- 12.4.2 The CIRB Operations Office develops and implements a plan for the notification of stakeholders as necessary of changes to the SOPs.

12.5 Availability of Policies and Procedures on the CIRB Website

- 12.5.1 The CIRB SOPs are posted on the public side of the CIRB website.