Title:	Multicenter Research and Reliance Process		
SOP Number:	901	Effective Date:	June 2, 2017
Previous Version Dates:			

1 Purpose

All non-exempt human subject research conducted under the auspices of the UNC-Chapel Hill must be reviewed and approved by the UNC Chapel Hill IRB or another designated IRB prior to the initiation of the research unless it has been determined that UNC-Chapel Hill is not engaged in the research. The authorized off-site IRBs that serve as the IRB-of-record for UNC-Chapel Hill have the same authority as the on-site IRBs and all determinations and findings of the off-site IRBs are equally binding on all research under the auspices of the organization.

In the conduct of cooperative research projects, UNC-Chapel Hill acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. It is the policy of UNC-Chapel Hill to assure that all facilities participating in a study involving human subjects receive adequate documentation about the study in order to protect the interests of study participants.

2 Procedure

2.1 Independent IRB and/or Central IRB

The University of North Carolina at Chapel Hill (UNC-Chapel Hill) IRB allows investigators to utilize one of six pre-approved Central IRB for industry-sponsored, multi-center, clinical research studies for which one of the six pre-approved Central IRBs have been appointed as the Central IRB by the Sponsor or CRO and the Central IRB has already approved (or is in the process of approving) the study. The use of a Central IRB is optional; investigators may wish to rely on an external IRB for some studies (e.g., Phase III) but not others (e.g., Phase I or II) or may choose to work with some Central IRBs but not others.

Investigator-initiated studies are not eligible for review by external IRBs; they must be reviewed by the UNC-Chapel Hill's IRB.

2.1.1 Investigator Responsibilities

1. Prior to submitting the application package to the external IRB, the investigator must satisfy the UNC-Chapel Hill application requirements for externally reviewed studies. An abbreviated IRBIS application must be completed in order for the UNC Chapel Hill IRB to confirm completion of all institutional requirements (e.g., radiation safety, COI disclosure, applicable training, data security) and for record-keeping purposes.

2. Per our agreements with the Central IRBs, the external IRB will invoice the Sponsor/CRO directly. UNC charges an additional preparation/processing fee which should be included in the study budget.

3. The UNC-Chapel Hill Responsibilities Prior to Accepting External Oversight for a Study

Following submission of the abbreviated application in IRBIS, the IRB reviews the following:

- Review application for completeness and consistency between sections
- Eligibility to use external IRB review (industry-sponsored)
- Review of investigator and study staff (confirmation of training and COI disclosure)
- Review of Institutional requirements (e.g., radiation safety, Investigational Drug Services (IDS) pharmacy)
- As privacy board: If applicable, adequacy of justification for limited waiver of HIPAA and if HIPAA Authorization form if free-standing (i.e., not embedded into the main consent document) is reviewed for required content.

Once the above are reviewed by the IRB and determined to be acceptable, the IRB issues the investigator a *Permission to Register/*contingency letter. The letter permits the investigator to move forward with their submission to the external IRB, provides additional information about the site registration process and may include additional UNC IRB stipulations (i.e., for institutional requirements.) Ancillary reviews include COI disclosure, managed by the Conflict of Interest Office and subject injury language (concurrence with the clinical trial agreement [CTA]) is managed by the Office of Industry Contracting. Both COI disclosure and subject injury language for Network Entity researchers is managed by the Network Entities Research Compliance office.

2.1.2 The UNC-Chapel Hill Responsibilities: Post External IRB Approval

Once the investigator has completed all requirements outlined in the Permission to Register/contingency letter and has registered with the Central IRB, the UNC IRB reviews the following:

- Response to stipulations, submission of applicable required documents (e.g., stand-alone HIPAA Authorization form) and completion of all required institutional requirements (e.g., Investigational drug service (IDS) pharmacy acknowledgement, Radiation safety committee approval)
- Review of the Central IRB-approved consent document:
    - Confirm congruency of subject injury language with documentation provided by the Office of Industry Contracting (OIC) or Network Entities Research Compliance office.

- If a COI has been disclosed, confirm congruency of consent form COI disclosure language with documentation provided by the COI Office or Network Entities Research Compliance office.

Investigators approved through external IRB review must still report local unanticipated problems, complaints, non-compliance, and an annual and end of study summary to the UNC-Chapel Hill IRB Office in addition to any external IRB reporting requirements. The addition of study personnel must be submitted to the UNC-Chapel Hill IRB prior to the personnel assuming any study responsibilities.

The external IRB must copy the IRB Office on all determinations of continuing or serious non-compliance and unanticipated problems involving subjects or others (UPIRSO). These will be reviewed by the UNC-Chapel Hill IRB Compliance Office.

Within 30 days of study expiration, the investigator must "renew" the study with the UNC IRB by completing submitting a renewal application that includes completion of a progress report and submission of the current approved consent forms and current external IRB approval letter. As with all studies, COI disclosure must be completed at least annually by applicable members of the research team.

2.2 National Cancer Institute's Central IRB Adult and Pediatrics Initiative

The UNC-Chapel Hill is a participant in the National Cancer Institute's Central Institutional Review Board (CIRB) Initiative for cooperative group protocols/studies that have been reviewed and approved by the CIRB. The UNC-Chapel Hill IO (or designee) submits the necessary documentation to maintain institutional registration with the CIRB, including the "Authorization Agreement/Division of Responsibilities", the listing of Key Personnel, and the "Annual Signatory Institution Worksheet About Local Context".

The CIRB defers responsibility to local institutions to conduct any reviews necessary under HIPAA. The CIRB does accept institutional boilerplate language for HIPAA authorizations if an institution incorporates authorization into the consent document.

UNC-Chapel Hill uses free-standing HIPAA authorizations for research; investigators should use the standard authorization form. Requests for a limited HIPAA wavier for use of PHI to identify and/or screen potential candidates should be submitted to the UNC IRB via IRBIS. The Lineberger Comprehensive Cancer Center (LCCC) NCI CIRB manager Office will include HIPAA authorization language when it submits the "Annual Signatory Institution Worksheet About Local Context".

The CIRB relies on local institutions to identify potential conflicts of interest and to develop conflict management plans. The UNC-Chapel Hill investigators should submit disclosures to the UNC Conflict of Interest office. Investigators must submit conflict management plans for themselves or members of the local research team to the CIRB using the "Study-Specific Worksheet About Local Context".

Investigators wishing to use the NCI CIRB must:

1. Contact the Lineberger Comprehensive Cancer Center (LCCC) NCI CIRB manager to request the materials necessary to register as an investigator with the CIRB.

2. Complete, on an annual basis, the "Annual Principal Investigator Worksheet About Local Context" and submit to the LCCC NCI CIRB manager and to the CIRB. Once CIRB-approved, the investigator may proceed with individual study applications.

3. In order to open individual protocols/studies under the CIRB, the investigator submits an application to the UNC-Chapel Hill IRB via IRBIS that includes the following:

   a. Study Summary and Key Personnel,
   b. Abbreviated IRB application,
   c. The protocol/research plan version, investigator brochure(s), and model consent currently approved by the NCI CIRB,
   d. The consent form for local use with required local institutional language incorporated,
   e. Translations of the consent form for local use with accompanying translation verification form,
   f. CITI Training is documented electronically for each member of the research team,
   g. Conflict of Interest disclosure is completed for applicable members of the research team, and
   h. The application is signed electronically by the principal investigator and department signatories.

4. The UNC-Chapel Hill IRB Office will review the abbreviated application, facilitate the COI review process, and provide a letter either accepting or declining CIRB oversight of the study (as a component of organizational approval).

   a. If accepted, the investigator may then proceed with the application to the CIRB by submitting the CIRB "Study-Specific Worksheet About Local Context". Note: If a member of the research team has a COI Management Plan, this must be submitted to the CIRB.

   b. If declined, a reason will be provided and the investigator will be given an opportunity to provide additional or clarifying information. In the event that the decision to decline is confirmed on re-review, the investigator may appeal the decision by contacting the IRB office.

5. Once approved by the CIRB, a copy of the CIRB approval must be submitted to the UNC-Chapel Hill IRB Office via IRBIS.

Ongoing responsibilities after study approval:

1. The UNC-Chapel Hill is responsible per written agreement with the CIRB to ensure compliance with the regulations governing research and the determinations made by the CIRB, and to report possible serious or continuing non-compliance and unanticipated problems to the CIRB for evaluation. In order to fulfill these responsibilities. The UNC-Chapel Hill needs to

maintain current documentation of the study, the actions taken by the CIRB, and any local issues that arise with the research. At least annually, the investigator will need to submit the following to the IRB office:

a. Amended protocols/research plans, investigator brochure(s), model and local consents, translated consents, and the associated documentation of CIRB approval;

b. Audit reports;

c. Local unanticipated events, protocol/research plan exceptions, and protocol/research plan deviations;

d. Local subject complaints or unresolved concerns;

e. Changes in local study personnel;

f. Changes in study status locally and study-wide (Open to Enrollment, Closed to Enrollment, Suspended, etc.);

g. Conflict of Interest disclosures on an annual basis or within 30 days of a change in significant financial interests or circumstances that could represent a conflict of commitment;

h. Current training records (CITI or accepted alternative) for each member of the local research team; and

i. An annual summary of study activity describing the number of local enrollees and status of enrollees (screen failure, on treatment, on follow up, withdrawn, complete, deceased), the study status (open to enrollment, closed to enrollment – active treatment, closed to enrollment – follow up only, closed to enrollment – data analysis, all local activities complete (closed)), any shifts in the evidence or in standard care that could impact the target study population or enrollment into the study, and any local complaints, concerns, or problems with the research.

2. The UNC-Chapel Hill IRB Office staff will review submissions and seek additional information, if needed, from the local research team. The UNC-Chapel Hill IRB Office will report potential unanticipated problems, potential serious or continuing non-compliance, local suspensions or terminations of research activities, and audit reports that note regulatory deficiencies to the CIRB. The report will include, if applicable, a corrective and preventative action plan (CAPA) developed in cooperation with the investigator. The CIRB will make a final determination regarding whether or not such events are unanticipated problems involving risks to subjects or others, serious non-compliance, or continuing non-compliance and will initiate any necessary reporting to sponsors and federal agencies.

3. Local investigators are responsible for submitting any COI management plans, translated consent forms (with accompanying certificate of translation), local subject materials, and local advertisements and recruitment materials to the CIRB.

4. Research open under the CIRB remains subject to the UNC-Chapel Hill and HRPP policies and procedures including, but not limited to, internal and external audits, training requirements, advertisements, privacy, and confidentiality.

2.3 Investigator-Initiated Collaborative Research

When employees or agents of the applicable UNC-CH conduct investigator-initiated non-exempt human-subjects research in collaboration with other institutions or with collaborating individual investigators as defined herein, each collaborating institution and/or collaborating individual investigator engaged in human-subjects research must obtain IRB approval for the research they are conducting. The OHRP guidance document *Guidance on Engagement of Institutions in Human Subjects Research* will be used as the basis for determining engagement in human-subjects research. Such determinations will be made by UNC IRB in collaboration and consultation with authorized representatives of the collaborating institution and/or the collaborating individual investigators, as applicable.

Investigators must specify in the UNC-CH IRB application the outside institutions and/or individuals involved in the research. Additional information required in the application is specified in OHRE's guidance document *How to Request a Reliance Agreement.*

2.3.1 Collaborating Institutions

Per relevant guidance from OHRP, when multiple institutions are engaged in the same non-exempt human-subjects research, the collaborating institutions may enter into joint review arrangements, rely upon the review of another qualified IRB, or make similar arrangements to avoid duplication of effort. When an institution is engaged in only part of the non-exempt human-subjects research, the institution must ensure that the part of the research project in which the institution is engaged is reviewed and approved by the institution's IRB or, on behalf of the institution, by another appropriately qualified IRB or Ethics Committee (EC). Alternatively, each institution may decide to review the entire research project, even if the information about the entire project is not necessary to approve the part(s) of the research in which the institution is engaged.

2.3.1.1 Reliance of Collaborating Institutions on the UNC-CH IRB

Collaborating institutions engaged in non-exempt human-subjects research may request to rely on the UNC-CH for review of the research. In such cases, the UNC-CH IRB will consider the request and, if it is granted, an IRB Authorization Agreement (IAA) also referred to as a Reliance Agreement must be executed by both institutions. The relying institution must have an active/approved FWA. In the absence of such a reliance arrangement, each institution will independently review the research project.

2.3.1.2 Reliance of the UNC-CH IRB on Collaborating Institution's IRB

UNC-CH may rely on the IRB of a collaborating institution. This may be because the majority of the non-exempt human-subjects research is being conducted at the collaborating institution, the collaborating institution's IRB has more relevant or specialized expertise and/or knowledge of the site where the research will be conducted, or because the collaborating institution has been designated as the sIRB (single IRB). In such cases, an IAA must be executed by both institutions. The institution relied upon for IRB review must have an active/approved FWA. In

the absence of such a reliance arrangement, each institution will independently review the research project.

2.3.1.3 Joint Review Arrangements

When UNC-CH IRB and the collaborating institution are each engaged in only part of a non-exempt human-subjects research project, each may decide to review only the part(s) of the project in which they are engaged. The UNC-CH IRB will make decisions about appropriate joint review arrangements depending on the circumstances of the particular project.

2.3.2 Collaborating Individual Investigators

When a collaborating individual investigator, whether an independent investigator or an institutional investigator, is engaged in non-exempt human-subjects research, UNC-CH may choose to extend its FWA to cover the collaborating individual investigator. In such cases, an Individual Investigator Agreement outlining the terms and conditions of this arrangement must be executed by both parties.

2.3.2.1 Disagreements among designated IRBs in multi-center research

The UNC-Chapel Hill IRBs welcome the input of IRBs at different institutions; however, the UNC-Chapel Hill IRB is ultimately responsible for the welfare of subjects at the University and must make decisions accordingly.

In research in which the UNC-Chapel Hill IRB has agreed to rely on another IRB for review of a given study, the UNC-Chapel Hill IRB has the authority to rescind this authorization at any time.