Recommendations for the Harmonization of Ancillary Reviews

Ancillary Reviews Working Group of the
SMART IRB Harmonization Steering Committee

November 2021

Harmonized: This document underwent a review and input process from April 2021 through October 2021 and has now been finalized.

CONTENTS

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

INTRODUCTION AND SUMMARY

The SMART IRB Harmonization Steering Committee's Ancillary Reviews Working Group (henceforth Working Group) considered the challenges ancillary reviews currently present to single IRB (sIRB) review and study activation timelines, which are detailed below, and identified four areas that represent opportunities to increase the efficiency of study activation:

1) Variations in the definition of ancillary reviews and identification of which reviews are relevant to sIRB review

2) Centralization of certain ancillary reviews for multisite studies

3) Timing of ancillary review requirements, particularly in relation to IRB review

4) The responsibilities of Reviewing IRBs, Relying Institutions, and study teams related to ancillary reviews

Specific best practice recommendations for each of these areas are presented below.

The Working Group did not make recommendations for the harmonization of which ancillary reviews an institution may require for human subjects research, because such reviews are usually study-specific and reflect variations in local research implementation requirements.

In addition to developing recommendations for best practices, the Working Group agreed that wide implementation of sIRB review provides institutions with the opportunity and incentive to reassess how their human research protection programs (HRPPs) approach ancillary reviews. Many institutions place the responsibility for identifying which ancillary reviews apply to a study on local IRBs (or local IRB offices), which then must also ensure that all or most of these requirements were met (e.g., by withholding final IRB approval until all ancillary reviews have been completed). Because most sIRBs are unwilling to take responsibility for ensuring Relying Institution ancillary reviews are completed, institutions may need to change their processes for identifying which ancillary reviews are required, how they ensure these reviews are accomplished, and at what timepoint the reviews should be completed.[1]

1. Prior to the National Institutes for Health (NIH) and the Common Rule sIRB requirements, when institutions relied on external IRBs, such as independent IRBs (aka "commercial IRBs") or the National Cancer Institutute Central IRB, their local IRB offices often conducted minimal review of the reliance requests and expected their researchers to identify applicable ancillary reviews and ensure they were completed. As institutions started to implement electronic review systems, they began to use these systems to identify and route research studies for applicable sign-offs. Although using these systems to support ancillary review requirements can increase compliance and efficiency, many systems are inflexible and do not take into account the use of an external IRB, nor how that review process differs from the process for local IRB review.

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

CHALLENGES WITH ANCILLARY REVIEWS

The Working Group agreed the ancillary review process can affect the efficiency of sIRB review and delay study activation. Examples of approaches that can adversely affect efficiency include:

- Some institutions withhold permission for their study teams to rely on an sIRB until all institutionally required ancillary reviews are completed. Such an approach can needlessly lengthen a Relying Institution's process to cede IRB review and hence the sIRB's review of that institution as a site.
- In response to increased requirements to use external IRBs, many institutions began leveraging their electronic IRB submission systems to identify required ancillary reviews and route studies to appropriate personnel or committees to complete their assessments. Some systems, however, are not flexible and require completion of all ancillary reviews before a certain timpoint, such as before IRB review. One consequence of such a system is that sIRB review can be delayed due to the time it takes to complete ancillary reviews that are not salient to that specific timeframe (e.g., requesting a reliance arrangement or the sIRB review of the site).
- Because of the gatekeeping function many local IRBs (or IRB offices) routinely perform on behalf of study teams, investigators who assume responsibility for ensuring the completion of required ancillary reviews are often unsure which reviews are required beyond IRB review and are unclear about the process for obtaining these reviews and when these reviews should occur in relation to IRB review or part of a reliance process. This confusion, which existed before the sIRB model but has been exacerbated by it, can lead to a delay in the submission and completion of ancillary reviews, especially when a specific review must occur prior to IRB review.
- Ancillary reviews take a different amount of time to be completed at each institution, which can negatively affect when relying sites can be reviewed and approved by the sIRB or when a study can be activated.
- Reviewing IRBs do not always communicate their expectations regarding what, if any, ancillary reviews conducted by a Relying Institution are relevant to their considerations and should be completed before they review a site.
- Under the sIRB model, it may not be clear which institution is responsible for ancillary reviews that may affect the study as whole. Moreover, some ancillary reviews may be unnecessarily duplicative and would benefit from being centralized, as has been accomplished for IRB review.

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

RECOMMENDATIONS

Ancillary Review Definitions

The Working Group developed definitions of ancillary reviews to promote use of consistent terminology across institutions. These definitions 1) distinguish between ancillary reviews and other information provided to an sIRB as part of local context considerations; and 2) identify ancillary reviews relevant to an sIRB's review versus those required before certain other timepoints, such as study actvation or enrollment of the first participant.

The Working Group recommends the adoption of the following definitions:

- **Ancillary reviews** are reviews that include signs-offs or approvals that are in addition to IRB approval of human subjects research and that are required by institutional or funding entity policy(ies) or by regulation, statute, or law. Ancillary reviews vary in whether they may occur before, during, or after IRB review, but most must be completed before site activation.
    - **Ancillary reviews relevant to sIRB review** are evaluations to ensure compliance with institutional, state and federal requirements that may have an impact on an sIRB's review and approval of a relying site, including any site-specific changes in study materials, such as the informed consent or recruitment documents. Ancillary reviews relevant to sIRB review should be provided to the Reviewing IRB before IRB review of that site occurs. Some ancillary reviews relevant to sIRB review continue to be required after IRB approval of the site. The primary example of an ancillary review relevant to sIRB review is conflict of interest (COI) assessment.
    - **Ancillary reviews required for other purposes** are evaluations performed to ensure compliance with institutional or funding entity policies, or by regulation, statute or law, that do not have an impact on sIRB review and approval of a relying site nor an effect on the content of study materials, such as informed consent or recruitment documents. Some ancillary reviews required for other purposes must be completed before a request is submitted to an sIRB to review that site or before study activation, while others must be monitored throughout the life of the study. Common examples of ancillary reviews required for other purposes include:
        - **Study feasibility reviews**, which are reviews performed to ensure a study can be conducted at an institution, such as assessments of facilities, study population availability, budget, and presence of or buy-in from support resources (e.g., nursing staff). These reviews often occur before a study team approaches their reliance contact about an sIRB arrangement or submits their site application for sIRB review.
        - **Non-IRB compliance reviews**, which are reviews that the institution responsible for the conduct of the research needs to ensure are completed before study activation or another related milestone (e.g., enrollment of the first participant), but which do not affect IRB review. Examples include a review of whether teams have completed other required trainings (e.g., Good Clinical Practice training for personnel engaged in some NIH-sponsored clinical trials), sign-off from a state agency to comply with state law (e.g., for radiation use or involvement of certain populations in research), or ensuring compliance with the FDA requirement to register clinical trials and report their results.

Ancillary reviews do not include cases where a Reviewing IRB can collect information via its application to make a determination or when Relying Institution reliance points of contact (POCs) can confirm a status or language based on their authority to a) interpret institutional policies (e.g., which study team personnel must complete institutionally required training) or b) apply institutionally agreed upon language (e.g., permitted compensation for injury language). For example, a Reviewing IRB can collect information as part of its application process to determine whether a study meets the NIH definition of a clinical trial and thus whether the informed consent document must include language about posting

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

information about the study at Clinicaltrials.gov. No ancillary review occurred in this instance. However, if an institution has a process independent of IRB review to determine whether a study should be defined as a clinical trial and requires the IRB to apply this assessment to a study, the determination of whether a study constitutes a clinical trial in this case would constitute an ancillary review and one that is relevant to sIRB review.

Centralizing Ancillary Reviews Relevant to sIRB Review

The Working Group encourages, when possible, the centralization of ancillary reviews relevant to sIRB review to avoid duplication of ancillary reviews conducted from the perspective of the overall study. A primary driver for adopting the sIRB model was to facilitate faster study activation by streamlining the IRB review process without adversely affecting human subject protection. This motivation can also be applied to ancillary reviews relevant to sIRB review. The concept of centralizing ancillary reviews is not new. Many oncology clinical trials coordinated through the NCI's cooperative groups, for example, already incorporate a centralized scientific review with local review concentrating only on study feasibility and resource availability to support the trial. In addition, several independent IRBs offer trial-wide institutional biosafety committee (IBC) reviews and coverage analysis services, and Harvard Catalyst developed an institutional biosafety committee (IBC) reliance authorization agreement similar to the SMART IRB Agreement[2]. This shift to centralized ancillary reviews may take efforts similar to those behind SMART IRB to build momentum for centralized review and potential regulatory or guidance changes, such as regarding IBC membership (e.g., unaffiliated members who represent the interest of surrounding communities).

As part of this shift to centralization, the Working Group acknowledges that some components of certain ancillary reviews may still need to occur locally to assess site-specific study implementation. Thus, centralized ancillary review means that one review occurs to cover all sites participating in a study. The centralized ancillary review does not need to be performed by an entity tied to the sIRB's institution and can be conducted by any of the participating institutions or an independent entity (e.g., commercial IBC services). Local ancillary review, on the other hand, pertains to assesments conducted by an institution relevant to its study implementation. For example, for some research a review by a single IBC to assess the risks of the overall study might be warranted. If a site requires additional IBC review, then that assessment may need to only focus on local study implementation (e.g., ensuring the facilities and procedures their study team will follow are adequate to conduct research safely).

Similar to what has been developed for sIRB reliance arrangements (e.g., the SMART IRB Agreement), institutions can enter into written agreements to rely on certain centralized ancillary reviews in total or in part in order to document the roles and responsibilities of the institution conducting the ancillary review and the institution relying on that review. The content and representations made within such documentation would depend on whether requirements are governed by specific regulations, such as the case for IBCs, or shaped by institutional policies. Table 1 provides examples of common ancillary reviews that could be centralized and describes how the components of these reviews can be parsed to separate the studywide and local components of the review to avoid duplication of efforts. Appendix 1 offers a template for documentation for the implementation of centralized ancillary review responsibilities.

2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7159810/

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

Table 1. Ancillary Reviews that can be Centralized for the Overall Study

Review Type	Elements of Centralized Review	Local Assessment
Scientific Review	Overall study design, endpoints, outcomes	Determination of study feasibility at the institutional level and of local study team qualifications
Institutional Biosafety Committee (IBC) Review	Assessment of research involving recombinant or synthetic nucleic acid molecules for compliance with the NIH Guidelines and potential feedback on informed consent language	Assessment of non-IRB related environmental health and safety issues for personnel (e.g., biological safety cabinet and bloodborne pathogen training); adequacy of laboratory space and facilities; and compliance with institutional requirements
Radiation Safety	Assessment of radiation risks posed by the overall study and adequacy of consent form language (taking into account potential variation in device radiation emission across sites)	Implementation of the study at the local institution, such as personnel expertise, training and licensing requirements; compliance with institutional requirements, procedures, and practices, and state law
Information Technology (IT) Security	Review of overall approach to ensure adequacy of any centralized data storage, expectations for data storage and transmission to ensure confidentiality; security of any device or software required by or evaluated as part of the overall study	Assessment of whether local data storage and transmission systems comply with institutional requirements
Clinicaltrials.gov	Assessment of whether a study meets the definition of an applicable clinical trial and of who is responsible for posting relevant information	None
Coverage Analysis	Identification and documentation of whether a study is a qualifying clinical trial that allows for billing certain study-required items/services to insurance pursuant to applicable laws and regulations; determination and documentation of billing designations for all patient care costs required by the study (i.e., identify routine costs that may be billed to a study participant and/or their insurer(s) vs. study costs for items/services that are primarily required for research purposes and that should be paid for by research funding and/or support)	Identification and assessment of any site-specific procedures not included in the studywide coverage analysis

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

Timing of Ancillary Reviews

The Working Group recommends that institutions carefully consider the timing of an ancillary review and not delay either a reliance arrangement or an sIRB's review of a site due to outstanding ancillary reviews that are not relevant to those processes. Ancillary reviews, for example, would not be expected to affect the execution of reliance agreements or documenting a reliance arrangement when a master reliance agreement, such as the SMART IRB Agreement, is used. Consequently, executing reliance agreements or documenting a reliance arrangment should never depend on completion of any ancillary reviews. Additionally, Relying Institutions should not require the completion of all ancillary reviews before agreeing that the sIRB can review their site, particularly when those ancillary reviews are not relevant to the sIRB review. Table 2 outlines the Working Group's recommendations regarding when ancillary reviews should be completed.

Table 2. Timing of Ancillary Reviews across a Study Life Cycle

Timeframe	Ancillary Reviews that should be Completed
Before a study team submits a request for a reliance arrangement	Reviews that assess whether a study can be performed at the institution (e.g., feasibility assessments, departmental sign offs, adequacy of facilities where research will be performed)
Before sIRB review and approval of a site	Reviews that could affect the sIRB's review of the study team, the site, and site-specific informed consent documents (e.g., language required to address a conflict of interest)
Before study activation	Reviews that do not affect IRB review but that the institution requires to be completed before a study can begin (e.g., ensuring study staff have undergone trainings other than human subjects protection training, such as those related to environmental health and safety or Good Clinical Practice; review of IRB-approved informed consent language to ensure consistency with contract obligations)
After study activation	Two categories of reviews may occur after a study has begun: 1) Those that are not tied to the IRB reliance or review process and could be or can only be completed after study activation (e.g., compliance with FDA clinical trial registration and results reporting; the Common Rule requirement to post a copy of a consent form used for clinical trials) 2) Those that are triggered as a result of changes to a study or events that occur during a study, which may affect local ancillary review and/or sIRB review of the site (e.g., addition of new study personnel with management plans for financial conflicts of interest relevant to the research)

The Working Group also considered several common ancillary reviews institutions require, including when these reviews should occur and whether they could directly affect sIRB review. Table 3 focuses on the types of ancillary review performed at Relying Institutions (or for a local study team that happens to be using the sIRB) that are not conducted for the overall study.

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

Table 3. Ancillary Reviews Performed by Relying Institutions for their Local Site and Relevance to sIRB Review

Type of Ancillary Review	Timeframe for Completion			Relevant to sIRB Review?
	Before Reliance is Initiated and Prior to sIRB Review	*After Reliance is Initiated but Before sIRB Reviews Site*	*After Reliance has been Executed*	
Affiliated hospital(s) committees[3]	✓			No
Research feasibility assessments, including local study team qualifications[4]	✓			No
Clinicaltrials.gov requirements		✓		Yes
Conflicts of interest (COI)		✓		Yes
Coverage analysis		✓		Yes
Privacy review[5]		✓		Yes
Institutional safety reviews, including radiation safety and biosafety[6]			✓	No
IT Security (e.g., data storage or transmission)			✓	No

3. Affiliated hospital committees determine if a study is feasible at a hospital associated with another organization (e.g., a university or academic medical center whose PI will lead the research study at those sites; examples of assessment include nursing support, facility access, drug and equipment availability, device purchasing, etc.).

4. Local scientific review comprises assessing research feasibility at that institution (e.g., the study has a sufficient number of participants, adequate resources and budget, and can be implemented logistically).

5. Privacy review includes situations such as a) when a local HIPAA privacy board must approve a waiver or alteration of authorization when the sIRB does serve as the privacy board; or b) if a Relying Institution uses a standalone HIPAA authorization form that requires sign off by a privacy officer (or similar function).

6. The most notable example includes environmental health and safety that ensures proper training and lab requirements at an institution. Many instituions leverage the IBC function to carry out the function of environmental health and safety. Separating the two functions is the key to acknowledging that while one can be deferred to an sIRB the other, environmental health and safety, should remain local but should not hold up sIRB review of the relying site.

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

Allocating Ancillary Review Responsibilities Related to an sIRB Arrangement

The Working Group agreed that promoting clarity of responsibilities related to ancillary reviews would increase efficiency in communication and processes and identified four groups that have responsibilities related to ancillary review under an sIRB arrangement. Specific recommended responsibilities for each group are outlined in Table 4.

Table 4. Ancillary Review Responsibilities Related to an sIRB Arrangement by Role

Group	Responsibilities
Reviewing IRB	The primary responsibilities of Reviewing IRBs regarding ancillary reviews involve communication. For sIRB arrangements, Reviewing IRBs should: • Communicate to Relying Institutions, including study teams, any specific ancillary reviews they expect to be completed before they review a site, what information from any required ancillary reviews should be provided to them, how this information is communicated, and when the information should be provided. • Identify any centralized ancillary reviews they will rely on prior to the review or approval of the overall study (e.g., scientific review external to the sIRB or IBC review of the protocol done by a central or independent IBC) and the scope of those assessments. • Only require the completion of ancillary reviews relevant to their assessment of that site (i.e., those that can directly affect their review or result in site-specific variations in study materials, such as informed consent documents). • Obtain an attestation from Relying Institutions (e.g., from reliance POCs via forms used to collect local context information) that any ancillary reviews that could affect their review of a site or their site's materials have been completed.
Relying Institutions	The challenges study teams experience with ancillary reviews existed before the implementation of sIRB review and occur even when local IRBs conduct reviews. Thus, these recommendations for Relying Institutions may also apply within the institution of the Reviewing IRB. Relying institutions should do the following to meet their obligations regarding ancillary reviews: • Identify the ancillary reviews they require (both those relevant to IRB review and others), when these reviews must be completed in regard to the key study life cycle timeframes identified above, which types of studies or study procedures the reviews apply to, the appropriate contacts for those reviews, and the review process (e.g., whether specific forms are required and how the review is initiated). • Identify the entities responsible for ensuring which ancillary reviews are completed, especially when they may be responsible for ancillary review compliance at different timepoints (e.g., reliance POCs may be assigned the responsibility of identifying and ensuring ancillary reviews relevant to IRB review are completed, but another office or person within the HRPP, such as research navigators or clinical trials offices, could ensure other ancillary reviews are in place before study activation). When possible, reliance POCs at Relying Institutions should ensure all ancillary reviews relevant to IRB review are completed before the sIRB reviews their specific sites.

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

Table 4. Ancillary Review Responsibilities Related to an sIRB Arrangement by Role (Continued)

Group	Responsibilities
Relying Institutions *(cont.)*	• Relying institution reliance POCs, as opposed site study teams, should communicate the outcomes of relevant ancillary reviews (e.g., conflict of interest management plans) to the sIRB as part of the local context considerations. • If ancillary reviews are identified by or routed through an electronic system, build flexibility into those processes so that reviews relevant to sIRB processes can be prioritized ahead of those that must be completed before study activation or later that are not relevant to IRB considerations. • Ensure processes are in place to identify a) when changes in research (e.g., protocol amendments), updates in study personnel, or other events (e.g., unanticipated problems or noncompliance) that occur after IRB approval may trigger ancillary reviews and b) how any ancillary review determinations relevant to sIRB review that occur after initial approval of a site will be communicated to the Reviewing IRB. These processes can include leveraging electronic submission systems to trigger ancillary reviews relevant to the overall study and sIRB's site oversight or could include using checklists or other tools to identify changes that would trigger an ancillary review. An example checklist of the types of changes or events that may trigger ancillary reviews potentially relevant to sIRB review is included in Appendix 2. • Ensure ancillary reviews occur in a timely manner and use flexible review processes when permitted, by allowing for sign off by a single individual versus a convened committee (when feasible and appropriate) and implementing strategies to facilitate ancillary reviews on ad hoc bases for time-sensitive research. • When an ancillary review has been performed in support of the study as a whole, as opposed to for a specific site, rely on those reviews when possible to eliminate duplicative effort, or only conduct the component(s) of the review relevant to site implementation of the study. Such arrangements may require additional reliance agreements or an addendum to a reliance agreement. See Table 1 for recommendations regarding which ancillary reviews or components of ancillary reviews might be centralized. • Ensure ancillary committees are aware of the scope of their review for ceded studies, especially any limits on the focus. • Create guidance for and educate study teams about ancillary reviews that are required for research studies in addition to IRB review.

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

Table 4. Ancillary Review Responsibilities Related to an sIRB Arrangement by Role (Continued)

Group	Responsibilities
Lead Study Team (or Coordinating Center)	If a multisite study involves a lead study team (or coordinating center) role, that team should: • Help Relying Site Study Teams understand the potential need for the completion of institution-specific ancillary reviews before their site is reviewed by the sIRB. • If responsible for preparing the IRB application for the site, ensure all relevant ancillary reviews have been completed that would affect the sIRB review of the site application. • Ensure the appropriate person has provided confirmation to the sIRB that relevant ancillary reviews have been completed.
Relying Site Study Team	A Relying Site Study Team should: • Identify the ancillary reviews relevant to their research at their institution. • Modify study template documents and other research materials (e.g., informed consent or other study materials) to reflect outcomes of relevant ancillary reviews, in consultation with the Lead Study Team, sIRB, and reliance POC, as appropriate. • Provide the outcomes of the ancillary reviews to their institutional reliance POC if the outcome of the review is not otherwise available to the reliance POC (e.g., via an electronic system). • Ensure ancillary reviews are completed by the appropriate timeframe of the study life cycle (e.g., before the study team submits a request for a reliance arrangement, before sIRB review and approval of a site, before study activation, after study activation). • Identify events that occur during a study or amendments that could trigger local ancillary reviews, and consult with personnel responsible for those reviews.

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

APPENDIX 1. IMPLEMENTATION CHECKLIST FOR CENTRALIZED ANCILLARY REVIEWS

The purpose of this checklist is to document any ancillary review responsibilities that one institution (i.e., a Reviewing Institution) will conduct on behalf of some or all sites participating in a multisite study. Of note, a Reviewing Institution for an ancillary review may or may not be the same as the Reviewing IRB Institution. Ancillary reviews are defined as evaluations performed to ensure compliance with institutional or funding entity policies, or by regulation, statute or law.

Who completes this checklist will vary depending on the number of ancillary reviews relevant to a study and which organization(s) will serve as the Reviewing Institution(s) for those ancillary reviews.

- If a single institution will act as the Reviewing Institution for all centralized ancillary reviews, then this institution should complete the checklist and ensure it is disseminated to all institutions relying on its review along with relevant supporting documents (e.g., additional reliance agreements when required).
- If there will be multiple Reviewing Institutions performing the different centralized reviews, then completion and distribution of this documentation is best coordinated by the Reviewing IRB, the Lead Study Team, or a coordinating center.

This checklist can be modified and tailored to a specific research study and may be used in conjunction with the SMART IRB Agreement Implementation Checklist and Documentation Tool, which covers ancillary reviews described within the SMART IRB Agreement, specifically related to conflict of interest and HIPAA Privacy Rule. Certain ancillary reviews, such as those conducted by an Institutional Biosafety Committee to comply with National Institutes of Health (NIH) requirements, may require additional documentation.

For further information, please see the SMART IRB Harmonization Steering Committee's complete guidance: *Recommendations for the Harmonization of Ancillary Reviews*.

Study Title:	
Overall PI:	
Site Investigator(s)	
Study ID No.	
Reviewing IRB:	
Relying Institution(s) for IRB review:	
Lead Study Team (if applicable):	
Date Completed:	

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

Review Type	Review Option
Scientific Review	☐ OPTION 1 – Review Not Centralized: All institutions engaged in this research study will perform scientific review pertaining to overall study design, endpoints, outcomes. ☐ OPTION 2 – Centralized Review: [NAME OF INSTITUTION] will serve as the Reviewing Institution for this ancillary review and will perform scientific review pertaining to overall study design, endpoints, and outcomes for the study. The other institution(s) engaged in this research study will only make determinations at the institutional level of study feasibility, local study team qualifications, etc. ☐ OPTION 3 – The institutions engaged in this research study have agreed on an alternate plan for scientific review (this may include some but not all institutions relying on centralized review). PLEASE DESCRIBE THE ALTERNATE PLAN:
Institutional Biosafety Committee (IBC) Review *NOTE: Ceding IBC review to another institution requires an IBC Authorization Agreement.*	☐ OPTION 1 – Review Not Centralized: All institutions engaged in this research study will assess research involving recombinant or synthetic nucleic acid molecules for compliance with the NIH Guidelines and potential feedback on informed consent language and non-IRB related environmental health and safety issues for personnel (e.g., biological safety cabinet and blood borne pathogen training), adequacy of laboratory space and facilities, and compliance with institutional requirements. ☐ OPTION 2 – Centralized Review: [NAME OF INSTITUTION] will serve as the Reviewing Institution for this ancillary review and will assess research involving recombinant or synthetic nucleic acid molecules for compliance with the NIH Guidelines and potential feedback on informed consent language, while the other institution(s) engaged in this research study will only assess non-IRB-related environmental health and safety issues for personnel (e.g., biological safety cabinet and blood borne pathogen training), adequacy of laboratory space and facilities, and compliance with institutional requirements. ☐ OPTION 3 – The institutions engaged in this research study have agreed on an alternate plan for IBC review (this may include some but not all institutions relying on the centralized review). PLEASE DESCRIBE THE ALTERNATE PLAN:

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

Review Type	Review Option
Radiation Safety	☐ OPTION 1 – Review Not Centralized: All institutions engaged in this research study will assess radiation risks posed by the overall study and adequacy of consent form language (taking into account potential variation in device radiation emission across sites). ☐ OPTION 2 – Centralized Review: [NAME OF INSTITUTION] will serve as the Reviewing Institution for this ancillary review and will assess radiation risks posed by the overall study and adequacy of consent form language (taking into account potential variation in device radiation emission across sites) while the other institution(s) engaged in this research study will only assess implementation of the study at the local institution, such as personnel expertise, training and licensing requirements; compliance with institutional requirements, procedures, and practices; and state law. ☐ OPTION 3 – The institutions engaged in this research study have agreed on an alternate plan for radiation safety review (this may include some but not all institutions relying on the centralized review). PLEASE DESCRIBE THE ALTERNATE PLAN:
Information Technology (IT) Security	☐ OPTION 1 – Review Not Centralized: All institutions engaged in this research study will review overall approach to ensure adequacy of any centralized data storage, expectations for data storage and transmission to ensure confidentiality, and security of any device or software required by or evaluated as part of the overall study. ☐ OPTION 2 – Centralized Review: [NAME OF INSTITUTION] will serve as the Reviewing Institution for this ancillary review and will review overall approach to ensure adequacy of any centralized data storage, expectations for data storage and transmission to ensure confidentiality, and security of any device or software required by or evaluated as part of the overall study, while other institution(s) engaged in this research study will only review local data storage and transmission systems' compliance with institutional requirements. ☐ OPTION 3 – The institutions engaged in this research study have agreed on an alternate plan for IT security review (this may include some but not all institutions relying on the centralized review). PLEASE DESCRIBE THE ALTERNATE PLAN:

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

Review Type	Review Option
Clinicaltrials.gov	☐ OPTION 1 – Review Not Centralized: All institutions engaged in this research study will assess whether a study meets the definition of an applicable clinical trial and who is responsible for posting relevant information. ☐ OPTION 2 – Centralized Review: [NAME OF INSTITUTION] will serve as the Reviewing Institution for this ancillary review and will assess whether a study meets the definition of an applicable clinical trial and who is responsible for posting relevant information. ☐ This review does not apply to this study.
Coverage Analysis	☐ OPTION 1 – Review Not Centralized: All institutions engaged in this research study will identify and document whether a study is a Qualifying Clinical Trial that allows for billing certain study required items/services to insurance pursuant to applicable laws and regulations and determine and document billing designations for all patient care costs required by the study (i.e., identify Routine Costs that may be billed to a study participant and/or their insurer(s) vs. Study Costs for items/services that are primarily required for research purposes that should be paid for by research funding and/or support). ☐ OPTION 2 – Centralized Review: [NAME OF INSTITUTION] will serve as the Reviewing Institution for this ancillary review and will identify and document whether a study is a Qualifying Clinical Trial that allows for billing certain study required items/services to insurance pursuant to applicable laws and regulations and determine and document billing designations for all patient care costs required by the study (i.e., identify Routine Costs that may be billed to a study participant and/or their insurer(s) vs. Study Costs for items/services that are primarily required for research purposes that should be paid for by research funding and/or support). The other institution(s) engaged in this research study will only identify and assess any site-specific procedures not included in the study-wide coverage analysis. ☐ OPTION 3 – The institutions engaged in this research study have agreed on an alternate plan for coverage analyses (this may include some but not all institutions relying on the centralized review). PLEASE DESCRIBE THE ALTERNATE PLAN:

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

APPENDIX 2. ANCILLARY REVIEWS THAT MAY BE TRIGGERED AFTER SIRB APPROVAL

The table below provides recommendations regarding when a change or event that occurs after sIRB approval of a site may require local ancillary re-review, as well as when the results of local ancillary reviews may need to be communicated to the sIRB. As identified in Table 2, ancillary reviews occur across the life cycle of a study.

Although many ancillary reviews related to IRB review occur before IRB review, some will be triggered after IRB approval, which means that institutions should to have processes in place to identify when these additional reviews must occur and when their outcomes should be communicated to the Reviewing IRB. Ancillary reviews that occur after IRB approval are typically prompted as a consequence of a reportable event or a change to a protocol or other study materials approved by the sIRB. However, not every event or change to the protocol and study materials will affect the Relying Institution's oversight of a study, nor will every change that requires local ancillary review or re-review generate information that needs to be reported back to the sIRB.

Changes/Events that may Trigger Ancillary Reviews after sIRB Approval

Change/Event	What May Trigger Local Ancillary Review	When sIRB May Need to be Informed
HIPAA-related events	• Change to a HIPAA form when a standalone document is used • Unauthorized/accidental breach of protected health information	• When new information in the HIPAA authorization would affect the informed consent document • If the breach requires communication with the research participants
Personnel Changes	• Need for confirmation of employment, licensure, skill training or compliance history of new personnel • Assessment of potential conflicts of interest (COIs)	• If personnel have limits on the roles they can assume related to a study or procedures they may perform • If a new COI management is issued that is relevant to the ceded research • PI change

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

Changes/Events that may Trigger Ancillary Reviews after sIRB Approval (Continued)

Change/Event	What May Trigger Local Ancillary Review	When sIRB May Need to be Informed
Administrative Study Procedures	• Changes affecting billable procedures that may require a new coverage analysis • Changes that will require the use of institutional resources not previously required (e.g., resources some institutional programs provide upon request, such as REDCap, biorepositories, clinical research units) • Changes that may affect study personnel safety, laboratory requirements • Changes that may require assessment of research personnel competence to perform procedures	• If local coverage analysis is conducted, any updates required to applicable informed consent documents
Pharmacy Support	• A protocol change that affects how drugs are dispensed or destroyed • A change in drug formulation or administration route poses risks to research personnel or others beyond research participants, such as family member exposure (e.g., evironmental health review may be triggered)	• If changes alter local pharmacy study charges, which could affect site informed consent language
Radiation Safety	• Changes in the amount of radiation, how it is delivered, the devices used to deliver radiation, or the population that will be exposed to radiation (e.g., minors) • Change in where the radiologic procedures are being performed • Personnel changes • Equipment changes • Changes in standard of care radiation procedures used on a study	• If changes affect site-specific materials, such as consent forms

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

CONTRIBUTING AUTHORS

John Baumann, PhD
Associate Vice President for Research Compliance
Indiana University

Judith Birk, JD
Director, IRBMED
University of Michigan

Nichelle Cobb, PhD
Senior Advisor for Strategic Initiatives, Association for the Accreditation of Human Research Protection Programs;
Senior Advisor, SMART IRB

Valery Gordon, PhD, MPH
Senior Advisor for Clinical Research
Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health

Kathy Lawry, MSSA, CIP, CIM
Senior Consultant
Association for the Accreditation of Human Research Protection Programs (AAHRPP)

Mike Linke, PhD, CIP
IRB Chair
University of Cincinnati

Helen Panageas, CIP
Director, IRB Operations
NYU Langone Health

Ada Sue Selwitz, MA
Executive Compliance and Integrity Advisor; Center for Clinical & Translational Sciences; Office of the VP of Research
University of Kentucky

Ivana Simic, PhD
Assistant Director, University of Florida IRBs
University of Florida

Jeanne Velders, JD, CIP
Executive Director, Human Research Protections Office
Washington University in St. Louis

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.

SMART IRB HARMONIZATION STEERING COMMITTEE LEADERSHIP

Barbara E. Bierer, MD
Director, Regulatory Foundations, Ethics, and Law Program, Harvard Catalyst
Director of Regulatory Policy, SMART IRB
Co-chair, SMART IRB Harmonization Steering Committee

Valery Gordon, PhD, MPH
Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health
Co-chair, SMART IRB Harmonization Steering Committee

Aaron Kirby, MSc
Director, Regulatory Affairs Operations, Harvard Catalyst
Director of Regulatory Operations, SMART IRB

Polly Goodman, CIP
Associate Director of Regulatory Affairs Operations, SMART IRB

Funded by the NIH National Center for Advancing Translational Sciences through its Clinical and Translational Science Awards Program, grant number 3UL1TR002541-04S2.