Recommendations for Harmonization of Post-Approval Auditing of Studies Subject to sIRB Review

Wednesday, November 18, 2020

2:00 – 3:30pm (EDT)

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Background

SMART IRB Agreement

Talks about compliance oversight and trial auditing:

- Participating institutions must, "…maintain, implement or have access to a human subjects research QA/QI process function, program or service that can conduct and report to the Participating Institution the results of for-cause and not-for-cause audits of the institution and its Research Personnel's compliance with human subjects protections and other relevant requirements."
- OR "must have an *alternate* means of monitoring the conduct of Research as appropriate to ensure compliance"
- OR "agree between or among themselves to waive the requirement"

SMART IRB Agreement

Mentions some expectations:

- Reviewing IRB
  - Make available upon request the Reviewing IRB's policies and procedures
  - Promptly notify a Relying Institution when conducting its own audit/investigation/allegation, and report findings within a reasonable timeframe.
  - May request the Relying Institution to conduct its own audit/investigation and report its findings back to the Reviewing IRB

SMART IRB Agreement

Mentions some expectations:

- Relying Institution
  - Ensure research personnel accept the decisions and requirements of Reviewing IRB and do not initiate changes to research without first receiving prior approval from Reviewing IRB (except where necessary to eliminate immediate hazards)
  - Promptly notify the Reviewing IRB of any unanticipated problems that may involve risk to human subjects, other noncompliance, and/or restrictions or suspension of research
  - Upon request from the Reviewing IRB, will conduct its own audit/investigation, or work cooperatively with Reviewing IRB to conduct an audit/investigation, and report its findings to the Reviewing IRB within a reasonable timeframe

SMART IRB Agreement

Does NOT talk about logistics or implementation strategies

SMART IRB Agreement

Let’s get real…

Case #1: Experience with sIRB Auditing - Not For Cause

- Site Principal Investigator and study team requested a not-for-cause audit due to:
  - Potential for FDA inspection
  - Reported confusion about sIRB process/responsibilities
- In the absence of guidance, Relying Institution's QA/QI Program:
  - Asked Reviewing IRB for study submissions & policies in order to conduct audit
  - Inter-institutional relationship strained due to misunderstandings about nature of audit & respective responsibilities
  - Escalated to HRPP leadership at both institutions

Case #2: Experience with sIRB Auditing - For Cause

- Lead Site holds IND and serves as Reviewing IRB
  - Lead Site reports multiple promptly reportable events in first year and extensive minor protocol deviations/minor noncompliance at first continuing review
  - Reviewing IRB notes no reporting (of any kind) from any other site

Case #2: Real Life Experiences with sIRB Auditing – For Cause

Reviewing IRB

Which is more likely?

- Only the lead site had protocol compliance issues?

OR

- Only the lead site understands what events need to be reported to the Reviewing IRB?

Result: Reviewing IRB determines that other participating sites will have a for-cause audit (note: first time this Reviewing IRB has made this request)

Case #2: Real Life Experiences with sIRB Auditing – For Cause

Lead site QA/QI Program asked to coordinate:

- IRB initially requested audit of two relying sites; requested audit findings to be reported by relying site within 3 months. Based on outcome of first two audits, IRB requested 5 additional site audits be conducted
- IRB's "audit request" sent to SMART IRB contacts
  - Provided site specific IRB history
  - Provided study specific audit questionnaire / report
  - Provided web link and specific relevant references to policies
  - Relying site QA/QI Program permitted to select % of subject review per local practice

Case #2: Real Life Experiences with sIRB Auditing – For Cause

Relying sites were given varying response times:

Round 1:

Request notice to first sites went out 67 days prior to requested response due date; audit specific materials provided 48 days in advance.

Round 2:

Request notice to remaining active sites (N = 5) with audit specific materials provided 65 days in advance.

Two sites asked for additional extension to conduct audit and return results. Both requested extension of 60+ additional days.

Case #2: Real Life Experiences with sIRB Auditing – For Cause

Outcome

- Every relying institution audit identified issues with study conduct or required documentation.
- Only half included draft CAPAs and additional time and/or submissions were needed to work through the CAPAs
- Approximately ¾ identified underreporting to Reviewing IRB.

Case #2: Real Life Experiences with sIRB Auditing – For Cause

Feedback from Relying Institutions:

- Site specific summary of IRB history was helpful, but also providing the actual IRB submission documents would have been better (tracked changes of ICS, etc.)
- More specific direction on the underlying potential concerns may have impacted approach or conduct of audit
- Extended notice and turn-around time preferred
- Interpretation of compliance with Reviewing IRB policy should remain with Reviewing Institution
- Relying sites could provide feedback about previous audits in lieu of re-auditing a previously reviewed investigator

Post-Approval Auditing Working Group

SMART IRB Harmonization Steering Committee (HSC):

Identifies an area in need of harmonization from community feedback and institutional experience

Forms working group of content matter experts to develop guidance, policy, or tool on assigned topic

Reviews completed project materials

Project Materials

Posted to SMART IRB website for public comment

Public comments reviewed by working group and edits made as necessary

HSC conducts final review

Posted for public use

Post-Approval Auditing Working Group – Background

1000s of protocols reviewed & approved by sIRB

Inconsistency in:

- Definitions of AEs, SAEs, noncompliance, serious and/or continuing noncompliance
- Which events are reported and reporting timelines
- QA/QI program structure, work processes and bandwidth

Relying institutions may have limited knowledge of protocol & Reviewing IRB's expectations

Shared Oversight

Reviewing IRB may have limited experience in sIRB, limited experience of relying institution, and limited enforcement provisions from a distance

Post Approval Auditing Guidance for Studies Subject to sIRB Review Working Group Membership

- Barbara Bierer, Harvard Catalyst + MRCT Center (Co-Lead)
- Jackie Do, Harvard Catalyst
- Kathy Lawry, Ambassador + AAHRPP
- Neala Lane, Indiana University (Co-Lead)
- Jason Malone, University of Washington
- Megan Singleton, Johns Hopkins University
- Sarah White, MRCT Center
- Jessica Williams, University of Kentucky

Post-Approval Auditing Working Group - Charge

Identify, propose and harmonize best practices and tools for the review of research through for-cause and not-for-cause audits of studies being conducted under a reliance agreement.

Outline for Recommendations

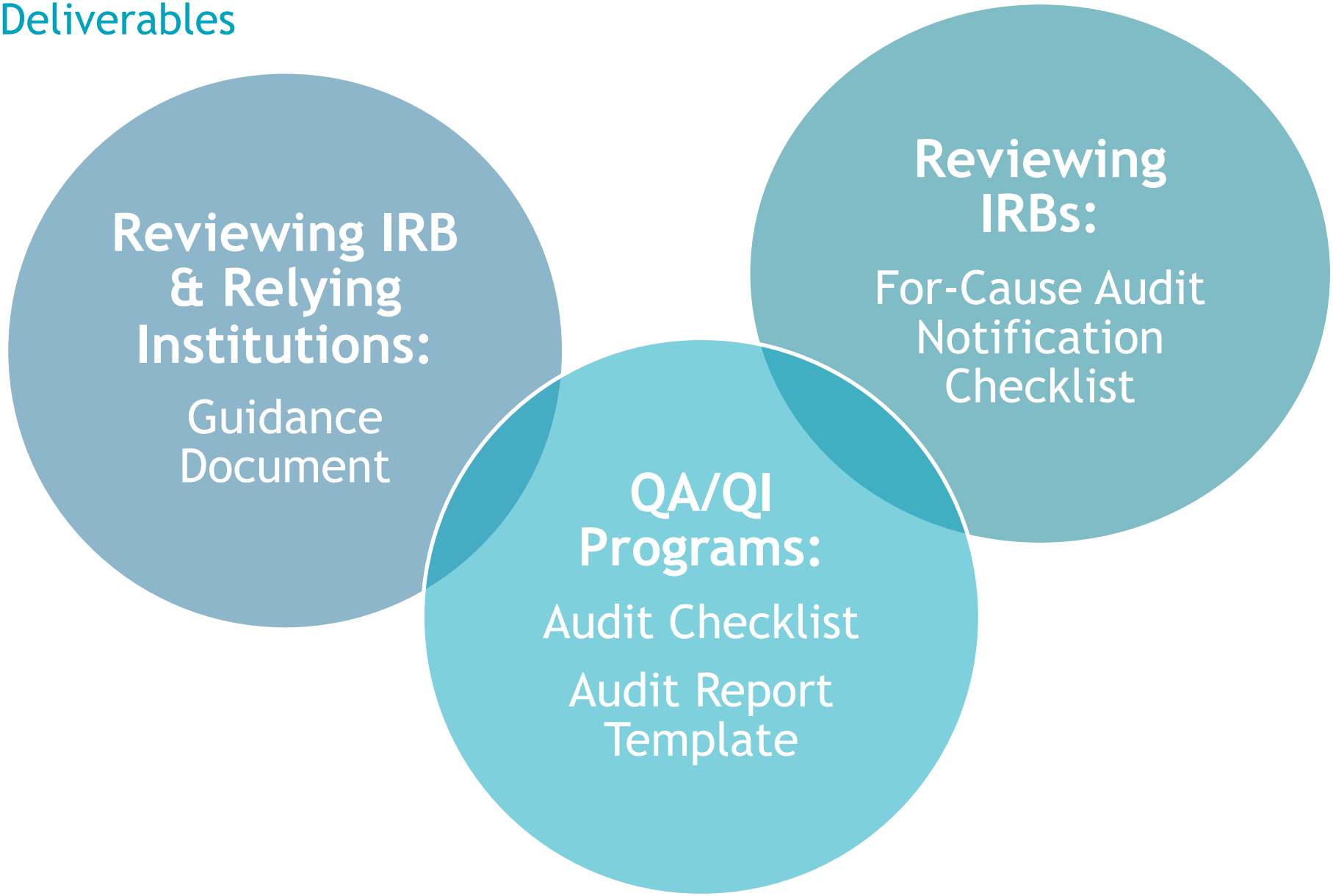
Not-For-Cause Audit

Conducted at the discretion of the Relying Institution as part of on-going post-approval monitoring program.

For-Cause Audits

Conducted at the request of the Reviewing IRB to obtain or verify information necessary to ensure compliance with the protocol, regulations, and/or institutional requirements.

Deliverables



For-cause Audits of studies subject to sIRB

For-Cause Audits

Reviewing IRB

- must define the scope of the audit
- must communicate the level and urgency of concern that prompted the audit request
- will determine the best method to perform the investigation along with the specific data and documents needed

For-Cause Audits - Rationale

Reviewing IRB has reason to suspect serious or continuing noncompliance:

- Information in the submission
- Report from an investigator, or other member of the study team
- Report from a third party. For example, participant or sponsor complaints, requests from Institutional Officials, or concerns from government agencies (e.g., FDA, NIH, OHRP).

Reviewing IRB has need:

- To verify that the protocol is being conducted in accordance with the IRB-approved protocol due to study specific considerations

For-Cause Audits – Notification Content

Information to be Communicated by Reviewing IRB:

- What concerns prompted the audit?
- What information is needed for the Reviewing IRB to make determinations?
- In what time frame should the audit be conducted and reported back to the Reviewing IRB?
- How will information be communicated between the Reviewing IRB and the Relying Institution?
- Who will perform the audit?

For-Cause Audit: Notification Procedures

- Reviewing IRB will send a written notice of the for cause audit request to the following
  - SMART IRB Institution Point of Contact (POC)
    - POC is expected to forward the audit request to the appropriate QA/QI staff at their institution, the director of the HRPP, director of the IRB, or institutional official consistent with institutional policy and confidentiality requirements.
  - Principal Investigator
  - Site-Responsible Investigator

For-Cause Audits: Review of Findings

- Within 30 calendar days of reviewing the audit findings, the Reviewing IRB should notify parties of their completed review.
  - Sent to Relying Institution's POC, Principal Investigator, and Site Investigator (as applicable)
  - Notification should identify the protocol; type of audit (e.g., for-cause, IRB requested), reason for audit and findings, and a summary of their review to be available upon request.
- The Reviewing IRB will provide the Relying Institution with an opportunity to review and comment on any corrective and preventative action plans.

Not-for-cause audits of studies subject to sIRB

Not-For-Cause Audits: Background

- Why should the **Relying Institution** conduct a not-for-cause audit of a study subject to sIRB (or any reliance agreement)?

Not-For-Cause Audits: Background

SHARED OVERSIGHT

Reviewing IRB retains responsibility for oversight of trial conduct

Relying Institution must ensure research personnel comply with the determinations and requirements of the Reviewing IRB(s), applicable federal regulations, all applicable state and local laws, and local institutional requirements related to the research

Not-For-Cause Audits: Background

- Why should the **Relying** (local) Institution conduct a not-for-cause audit of a study subject to sIRB (or any reliance agreement)?
  - Because you may have limited information about the ongoing research study
  - There may be differences in reporting requirements
  - Culture of institution and IRBs may be different
  - *The institution is responsible for compliance*

Not-For-Cause Audits

The guidance document recognizes that institutions have their own ongoing post-approval monitoring program

- Not-for-cause audit program – protocol meets criteria per local policies.
- Investigator requests an audit for education or quality improvement purposes.

Supports the **Relying Institution** including studies subject to sIRB as part of their on-going program

Reviewing IRB should not demand a not-for-cause audit

Not-For-Cause Audits: **Conducting the audit**

Process for tracking studies that are under a reliance agreement

- Automatic or manual depending on your local processes

Collection and review of documents

- Relying Institution should ask the study team first or, if necessary
- Reviewing IRB to provide the necessary documents in order to perform
- Relying Institution may reach out to Reviewing IRB for assistance on the interpretation of Reviewing IRB's policies.

Not-For-Cause Audits: **Reporting the Results**

Local Investigator

- Report of audit will be provided per the Relying Institution's policy.

Reviewing IRB

- Report of audit is optional if no suspected reportable events or serious and continuing non-compliance are discovered
- Report of audit is required if any suspected issues of potential serious or continuing non-compliance of

The Reviewing IRB will be responsible for determining if further investigation is necessary

Reviewing IRB Responsibilities :

COMMUNICATION to the Relying Institution

What is the concern?
Is there an urgency?

DETERMINATION of whom will perform the audit

Reviewing IRB
Relying Institution
Trusted 3rd party

The **TIME FRAME** for completion of the for-cause audit

A **PROCESS** for sharing study documents

In a manner efficient/effective for the institution conducting the audit

DEVELOP an appropriate corrective action plan

(And share with Relying Institution before finalizing)

Relying Institution Responsibilities :

CONDUCT the for-cause audit as requested; PROVIDE a written report

PROVIDE FEEDBACK to the Reviewing IRB and investigator(s) on the Corrective Action Plan

COMMUNICATE any issues of potential serious and continuing noncompliance

PROVIDE relevant study documents and policies

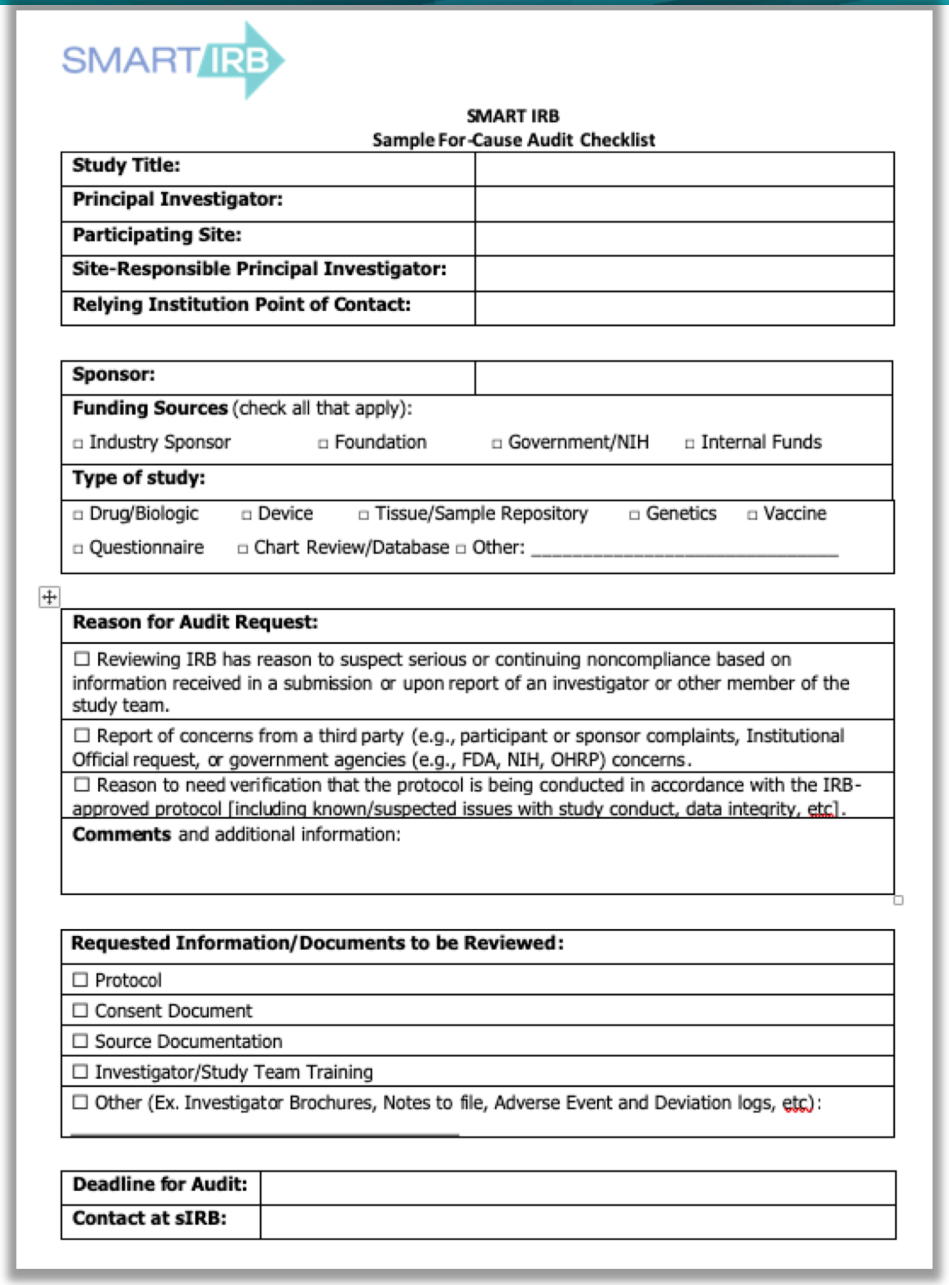
CONDUCT not-for-cause audits regularly as part of their post-approval monitoring program

Open Communication is Important

- Relying Institutions need to:
  - Communicate ability to provide quality assurance/quality improvement to ongoing studies
  - Capacity to conduct an onsite audit (or upon whom it will rely)
- When questions arise during the course of a study, open communication is key as often clarification or a simple verification of some documentation may suffice to resolve an issue

Action Plan

A For-Cause Audit Checklist has been developed to streamline the request process and collection of data.



SMART IRB

SMART IRB
Sample For-Cause Audit Checklist

Study Title:	
Principal Investigator:	
Participating Site:	
Site-Responsible Principal Investigator:	
Relying Institution Point of Contact:	

Sponsor:	

Funding Sources (check all that apply):

□ Industry Sponsor □ Foundation □ Government/NIH □ Internal Funds

Type of study:

□ Drug/Biologic □ Device □ Tissue/Sample Repository □ Genetics □ Vaccine

□ Questionnaire □ Chart Review/Database □ Other: _____

Reason for Audit Request:
☐ Reviewing IRB has reason to suspect serious or continuing noncompliance based on information received in a submission or upon report of an investigator or other member of the study team.
☐ Report of concerns from a third party (e.g., participant or sponsor complaints, Institutional Official request, or government agencies (e.g., FDA, NIH, OHRP) concerns.
☐ Reason to need verification that the protocol is being conducted in accordance with the IRB-approved protocol [including known/suspected issues with study conduct, data integrity, etc].
Comments and additional information:

Requested Information/Documents to be Reviewed:
☐ Protocol
☐ Consent Document
☐ Source Documentation
☐ Investigator/Study Team Training
☐ Other (Ex. Investigator Brochures, Notes to file, Adverse Event and Deviation logs, etc):

Deadline for Audit:	
Contact at sIRB:	

Sample Audit Checklist for use by auditing QA/QI team

SMART IRB

Sample Audit Checklist

for use by auditing QA/QI team

A. REGULATORY DOCUMENTATION

1. Is the approved protocol on file? (Original and all previously approved versions?) ▫Yes ▫No

1.1 Is the IRB Approval Letter(s) on file? ▫Yes ▫No

1.2 Is this an FDA regulated study? (If no, go to 1.3) ▫Yes ▫No ▫NA

1.2.1 Is there a signed FDA 1572 on file? ▫Yes ▫No

1.2.2 Are all versions of the Investigator Brochure or package insert on file? ▫Yes ▫No

1.2.3 Are all versions of the package insert or device manual on file? ▫Yes ▫No

1.2.4 Is all correspondence to and from the FDA on file? ▫Yes ▫No

1.3. CVs of PI/Co-PI and all study staff on file? ▫Yes ▫No ▫NA

1.3.1 For all CVs on file, are they current in alignment with applicable requirements? ▫Yes ▫No

1.3.2 For all CVs on file, are they signed and dated, if required? ▫Yes ▫No

1.3.3 Is there a staff training log? ▫Yes ▫No

1.3.4 Is the staff training log complete and up-to-date? ▫Yes ▫No

1.4. Is there a subject enrollment log? ▫Yes ▫No

1.4.2 Is the subject enrollment log complete? ▫Yes ▫No

1.5. Is/will the site (be) monitored? ▫Yes ▫No

1.5.1 Who is the monitoring body? _____

1.5.2 How often? _____

1.5.3 Is there a monitoring log? ▫Yes ▫No

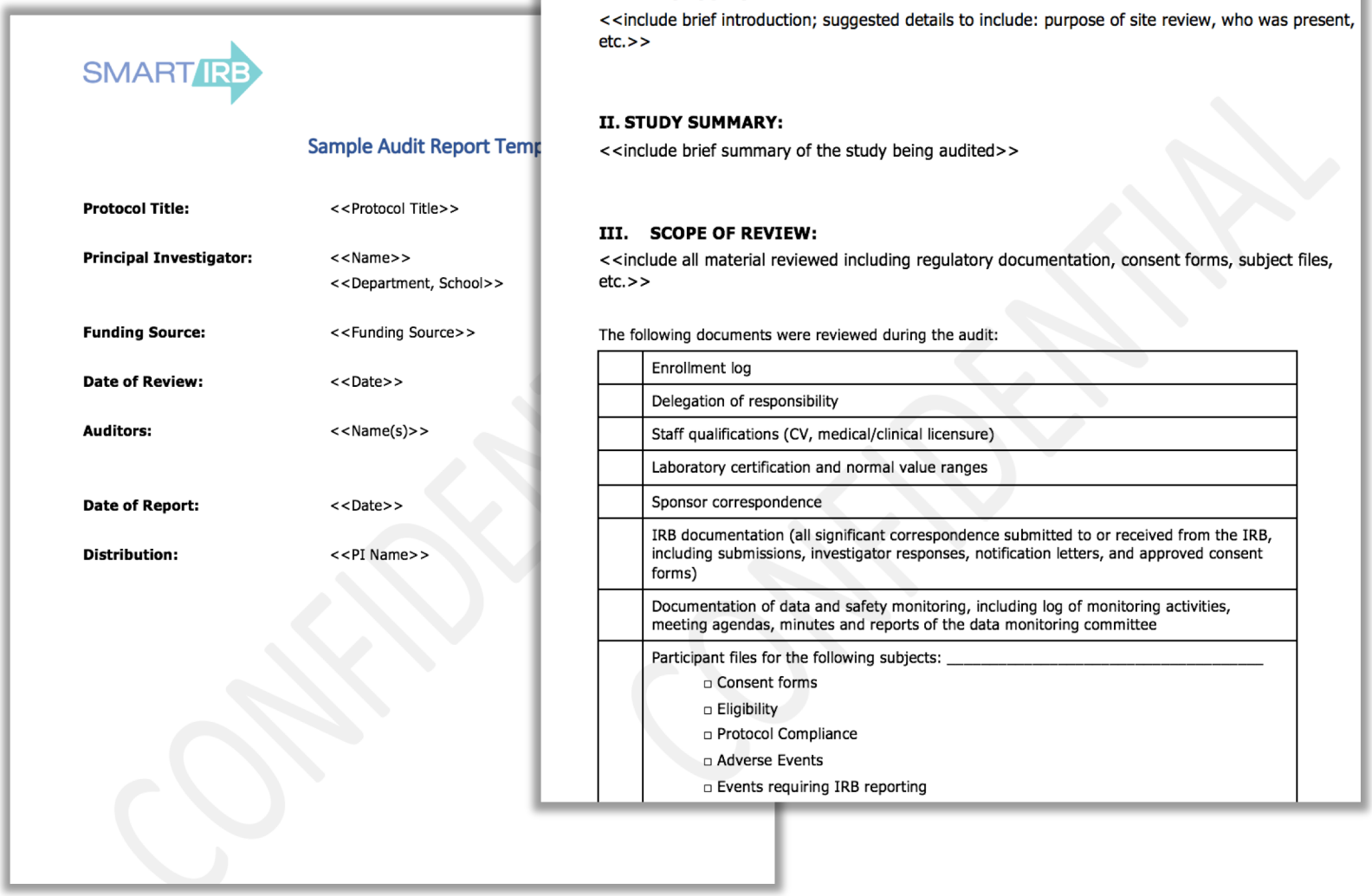
1.5.4 If yes, is the monitoring log complete? ▫Yes ▫No

1.6 Is there a staff signature and delegation of responsibilities log? ▫Yes ▫No ▫NA

1.6.1 Is the staff signature and delegation log complete and up-to-date? ▫Yes ▫No

1.7 Is all correspondence to and from the sponsor on file? ▫Yes ▫No ▫NA

Sample Audit Report Template



SMART IRB

Sample Audit Report Temp

Protocol Title:	<<Protocol Title>>
Principal Investigator:	<<Name>> <<Department, School>>
Funding Source:	<<Funding Source>>
Date of Review:	<<Date>>
Auditors:	<<Name(s)>>
Date of Report:	<<Date>>
Distribution:	<<PI Name>>

SMART IRB

I. INTRODUCTION:

<<include brief introduction; suggested details to include: purpose of site review, who was present, etc.>>

II. STUDY SUMMARY:

<<include brief summary of the study being audited>>

III. SCOPE OF REVIEW:

<<include all material reviewed including regulatory documentation, consent forms, subject files, etc.>>

The following documents were reviewed during the audit:

	Enrollment log
	Delegation of responsibility
	Staff qualifications (CV, medical/clinical licensure)
	Laboratory certification and normal value ranges
	Sponsor correspondence
	IRB documentation (all significant correspondence submitted to or received from the IRB, including submissions, investigator responses, notification letters, and approved consent forms)
	Documentation of data and safety monitoring, including log of monitoring activities, meeting agendas, minutes and reports of the data monitoring committee
	Participant files for the following subjects: _____ □ Consent forms □ Eligibility □ Protocol Compliance □ Adverse Events □ Events requiring IRB reporting

Discussion & questions