SINGLE IRB CONTINUING REVIEW PROCESS:

Recommendations for Harmonization

Continuing Review Working Group of the
SMART IRB Harmonization Steering Committee

October 15, 2020

For review only; document is not finalized.

CONTENTS

INTRODUCTION

The SMART IRB Harmonization Steering Committee's Continuing Review Working Group (henceforth Working Group) examined the effect of single IRB on continuing review, with the goal of recommending potential areas for harmonization amongst institutions, IRBs, and study teams. These recommendations focus only on formal continuing review processes, defined as the requirement for IRBs to review research "at intervals appropriate to the degree of risk, not less than once per year" [45 CFR 46.109(e), 21 CFR 56.109(f)]. This guidance does not cover institutional oversight of research not subject to continuing review.

The Working Group acknowledges that the processes and expectations established as part of a study's initial review have implications for continuing review, including:

- Who is responsible for providing information for the continuing review to the Reviewing IRB (e.g., a lead study team, a coordinating center, site investigators, study sponsor, or combination of these sources)
- What information is provided to the Reviewing IRB for continuing review
- Whether the study has a sponsor or data coordinating center to oversee the collection of studywide data and events (e.g., adverse events, unanticipated problems, protocol deviations) or whether this responsibility resides with a lead study team
- The systems (e.g., electronic vs. paper) used by the Reviewing IRB to collect and store study information, which can affect the level of information or documents study teams may be required to provide
- Whether the study will be overseen by a data and safety monitoring board (DSMB) or data monitoring committee (DMC), or whether another mechanism is used to monitor for trends related to subject safety, such as unexpected risks

The Working Group's recommendations consider these processes and expectations and identify the relative roles and responsibilities of the Reviewing IRB, Relying Institutions, and study teams regarding continuing review. The recommendations presume the existence of an Overall Principal Investigator (PI) (also called a Lead Investigator) or equivalent role. The Overall PI must know what information the Reviewing IRB requires for the continuing review, and must communicate these requirements to site investigators and put in place processes to collect and synthesize that information to provide it to the IRB. Many IRBs that serve as a single IRB require the Overall PI designate a lead study team, which could be a coordinating center, that is responsible for communication with the Reviewing IRB. Moreover, a designated lead study team plays a critical role in ensuring that participating sites comply with the IRB-approved study and IRB determinations and promptly communicate events and other information for potential reporting to the Reviewing IRB, so that the IRB has sufficient information to adequately oversee the research. The Working Group's recommendations for the information that an Overall PI should ensure is collected and provided to the Reviewing IRB parallel the information that would be required for the Overall PI to monitor the study and for other reporting, such as to a funding agency, sponsor, or the FDA. Because the use of single IRB often increases investigator responsibilities, the Working Group urges institutions to make resources (e.g., coordinating center personnel and DSMBs) available to investigators who conduct multisite studies, or to assist them in obtaining funding to ensure effective communication between sites and oversight of study progress, adverse events, and protocol deviations.

REGULATORY BASIS OF CONTINUING REVIEW

Federal regulations do not indicate what information an IRB must consider as part of the continuing review processes. The Common Rule, for example, simply states that an IRB:

- *Must establish and follow written procedures for*
    - *conducting its continuing review of research and for reporting its findings and actions to the investigator and the institution [§46.108(a)(3)(i)]; and*

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- *determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review [§46.108(a)(3)(ii)].*
- *Shall conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk, not less than once per year with some exceptions [§46.109(e)].*

US Food and Drug (FDA) regulations generally mirror the Common Rule regarding continuing review, including documentation requirements, except that, as of this guidance's drafting, they do not allow research to be excused from continuing review.

Because of the lack of detail within the regulations, institutions generally follow the detailed guidance provided by the Office for Human Research Protections (OHRP)[1] and the FDA[2] regarding their expectations for an IRB's conduct of continuing review. The FDA and OHRP guidance documents (henceforth collectively referred to as "the guidance") make it clear that continuing review serves two purposes: 1) to ensure the rights and welfare of research subjects continue to be protected by ensuring the research continues to meet the criteria for IRB approval; and 2) to ensure investigators and their study teams are in compliance with the determinations and requirements of the Reviewing IRB (e.g., they are using the most recently approved versions of the informed consent documents and are not enrolling more participants than approved by the IRB). Consequently, the information IRBs collect to perform continuing review should allow them to assess the criteria both for IRB approval and for study team compliance**.** Table 1 identifies the information IRBs should collect from investigators for the continuing review process and identifies which aspect of continuing review each category of information addresses.

The guidance states that Reviewing IRBs should start with the working presumption that the research continues to satisfy all the criteria for IRB approval. This assumption should be verified through the examination of the following four aspects of the research:

1. Risk assessment and monitoring, which includes a consideration of
    - Any new information that would alter previous IRB determinations related to risk minimization and risks being reasonable in relation to anticipated benefits
    - Unanticipated problems that have occurred
    - Whether any safety monitoring that was required as part of the prior approval of the research has been implemented and is effective
2. Adequacy of the process for obtaining informed consent, which includes
    - Verification that
        - The investigator is using the most recently approved version of the informed consent document;
        - Informed consent document(s) contain the most accurate, up-to-date information about the research; and
        - The currently approved consent document(s) adequately addresses the elements of informed consent
    - Identification of whether there is any new information presented by the investigator or others that raises concerns about the circumstances under which informed consent is being obtained
    - Determination regarding whether any significant new findings have occurred and should be provided to participants

[1] Office for Human Research Protections (2010). Continuing Review Guidance. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/index.html
[2] US Food and Drug Administration (February 2012). IRB Continuing Review after Clinical Investigation Approval. https://www.fda.gov/media/83121/download

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3. Investigator and institutional issues, which includes an assessment of
    - Changes in the investigator's situation or qualifications (e.g., suspension of hospital privileges, change in medical license status, or increase in number of research studies conducted by the investigator)
    - The evaluation, investigation, and resolution of any complaints related to the investigator's conduct of the research
    - Changes in the acceptability of the proposed research in terms of institutional commitments (e.g., personnel and financial resources, adequacy of facilities) and applicable regulations, state and local law, or standards of professional conduct or practice
    - Reports from any third-party observations of the research
4. Research progress, which includes
    - Confirmation that the information provided by the investigator at the time of continuing review is consistent with the research protocol previously approved by the IRB
    - Evaluation of the number of subjects enrolled in the research to ascertain whether enrollment is consistent with the planned number of subjects described in the IRB-approved protocol
    - Review of subject withdrawals and the reasons they occur

Although the guidance provides Reviewing IRBs with a more detailed roadmap regarding how to conduct continuing review, some recommendations within the guidance lack clarity, especially when applied to the single IRB context. In putting together its recommendations for continuing review, the Working Group explored some of the challenges the guidance presents, especially in regard to the four key considerations outlined above.

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Table 1. OHRP and FDA guidance regarding the information IRBs should review as part of a continuing review

Category of Information	Relevant aspect of continuing review			
	Risk assessment and monitoring	*Adequacy of the process for obtaining informed consent*	*Investigator and institutional issues*	*Research progress*
A brief project summary				X
The number of subjects accrued (for multicenter research studies, the number of subjects accrued at the local institution and the number accrued study-wide, if available, should be provided)	X	X		X
A brief summary of any amendments to the research approved by the IRB since the IRB's initial review or the last continuing review	X			X
Any new and relevant information, published or unpublished, since the last IRB review, especially information about risks associated with the research	X	X		X
A summary of both any unanticipated problems and available information regarding adverse events	X	X		
A summary of any withdrawal of subjects from the research since the last IRB review, and the reasons for withdrawal, if known	X	X		X
A summary of any complaints about the research from subjects or others since the last IRB review	X	X	X	X
The latest version of the IRB-approved protocol and sample informed consent document(s)		X		
Any proposed modifications to the informed consent document or protocol	X	X		
For FDA-regulated research, the current Investigator's Brochure, if available, including any modifications	X			
Any other significant information related to subject risk, such as the most recent report from any DSMB or DMC monitoring the research, if available	X			

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Risk Assessment

The guidance indicates that Reviewing IRBs should be able to identify at continuing review any new information that would alter previous Reviewing IRB determinations related to risk minimization and risks being reasonable in relation to anticipated benefits. Most likely, such information will be discovered outside of the continuing review process through the submission of amendments and reportable events. However, continuing review can be leveraged as an opportunity to prompt study teams to systematically consider study events and other information to assess whether any alterations have occurred to the risks, benefits, and alternatives to the research.

The guidance suggests that the Reviewing IRB should require the submission of a summary of any unanticipated problems and available information regarding adverse events that have occurred. Such a list of events may not be necessary, however, for the Reviewing IRB to receive when the study has a DSMB or DMC, which would track and analyze these events. In contrast to a DSMB or DMC, the Reviewing IRB often is unable to assess safety trends, because they may not have the statistical expertise that a DSMB or DMC has or access to information about which group subjects are assigned to in the case of blinded research. When a study's data monitoring plan includes the use of a formal DSMB or DMC, however, the Reviewing IRB should obtain DSMB or DMC reports to ensure the committee convenes as expected and can rely on those reports to monitor for any concerning adverse event trends.

When a study does not have a DSMB or DMC and may pose more than minimal risk to subjects, Reviewing IRBs need to ensure the data monitoring plan approved for a study will assure events that occur are being appropriately identified, evaluated, and categorized so that unanticipated problems are promptly reported to the IRB for an assessment of potential impact on study risks. The Reviewing IRB can then confirm at continuing review that any required data monitoring plan has been implemented and effective, such as by requesting the lead study team provide an assessment of adverse events to identify potential changes in risks to subjects based on the frequency or severity of the events. Consequently, the lead study team must set up mechanisms to collect the appropriate information from site investigators and have processes in place to periodically assess the adequacy of the monitoring.

Some Reviewing IRBs require the inclusion of a list of unanticipated problems and adverse events as part of the continuing review. However, there are more effective methods to perform a compliance function (i.e., to ensure that all potential unanticipated problems have been reported). For example, post-approval monitoring programs can conduct audits to determine whether study teams are reporting the events a Reviewing IRB requires or the continuing review form could include a question that prompts study teams to provide or identify information not previously reported.

Adequacy of the Process for Obtaining Informed Consent

The guidance includes multiple expectations surrounding informed consent. Reviewing IRBs are expected to ensure the following:

- Study teams are using the most recently approved informed consent document and conducting an appropriate informed consent process,
- The informed consent documents continue to be accurate and include the appropriate elements of consent, and
- Any significant new findings that should be communicated to participants are identified.

In the case of single IRB review, the Working Group noted that some of these functions become more complex. For example, to confirm that study teams are using the most current IRB-approved consent documents, should the Reviewing IRB collect and review consent documents from each participating site? Should this responsibility instead be assigned to the Overall PI? Or, can auditing processes or electronic review systems be leveraged instead? Many IRBs use their electronic systems to ask study teams to confirm that the documents within that

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system are those that have been used and identify which document(s) require reapproval. If copies of consent forms are collected by the Reviewing IRB, participant information should be redacted, and a copy used by each of the sites collected for review. The Working Group agreed that Reviewing IRBs could use different methods, including a combination of them, to ensure study teams are using the correct versions of informed consent documents.

The guidance does not explicitly describe how Reviewing IRBs might assess the circumstances under which investigators and their study teams obtain informed consent. Although the guidance recommends IRBs review the latest version of the sample informed consent document(s), this approach can only reveal whether study teams are using that version and does not speak to the informed consent process. Consequently, Reviewing IRBs may need to ask for auditing and post-approval monitoring reports at continuing review in part to help identify potential concerns with the informed consent process, and may need to explicitly instruct the lead study team to collect information about consent process issues and provide that information at continuing review, if not sooner. Moreover, the expectation that Reviewing IRBs be able to identify concerns with the consent process at continuing review underscores the importance for IRBs to require at initial review a sufficiently detailed description of the proposed consent process as well as the qualifications and training of those who will obtain informed consent to ensure a robust process is approved.

In regard to any significant new findings that have occurred and may need to be communicated to participants, such information would likely be provided to a Reviewing IRB prior to continuing review as an amendment or reportable event. Continuing review, however, is an opportunity to encourage the Overall PI to identify and assess whether any new and relevant information has arisen since the last IRB review that has not been previously reported and to review events that have occurred to determine if they suggest new information should be communicated to participants. Consequently, the Working Group recommendations describe the Overall PI as having responsibility for providing the Reviewing IRB at continuing review with any new information, published or unpublished, that could affect the study (particularly research risks, benefits, alternatives to participation) or informed consent documents.

Investigator and Institutional Issues

It is less clear from the guidance what information the FDA and OHRP recommend IRBs obtain for continuing review, aside from a summary of subject complaints, that would allow them to assess investigator and institutional issues. When addressing continuing review, many reliance agreements, including the SMART IRB Agreement, describe institutional and investigator issues and tend to focus on: whether investigators and their study teams have the time, resources, and qualifications to conduct the research; any state and local laws or standards of professional conduct or practice that could affect the research; any changes in the conflict of interest (COI) status or management plans for newly added study personnel; and whether any audits have identified issues of concern.

Similarly, the Working Group recommends that Reviewing IRBs obtain from Overall PIs an attestation that none of the participating investigators' situations or qualifications have changed in ways that would adversely affect their participation in the study; no changes have occurred in the acceptability of the proposed research for each of the participating sites in terms of institutional commitments and applicable regulations, state and local law, or standards of professional conduct or practice; and no changes have occurred in the COI status or management plans for personnel added to or removed from the study. Overall PIs thus must put in place mechanisms to collect this information from relying site study teams and Reviewing IRBs must have processes to ensure this information is communicated to them. In addition to attestations from the Overall PI about the relying site investigators, the Reviewing IRB also should ensure it confirms that any relevant auditing or monitoring reports (i.e., those that identify events that would require reporting to the IRB) already have been submitted for review or are provided at continuing review.

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Research Progress

The guidance focuses on two aspects of research progress: confirming that the information provided by the investigator at the time of continuing review is consistent with the research protocol previously approved by the IRB and evaluating the number of subjects enrolled in the research to ascertain whether enrollment is consistent with the planned number of subjects described in the IRB-approved protocol. Per the guidance, a marked difference between the actual and expected rates of enrollment may indicate a problem with the research project that requires further evaluation, including whether the research project is likely to provide sufficient data to answer the scientific question(s) being posed. Although the guidance does not specifically refer to DSMB/DMC reports as important for the evaluation of study progress, these committees can identify whether a project needs a course adjustment or should be stopped early, which is one of the reasons why Reviewing IRBs must ensure they obtain these reports. The Working Group agreed that the Reviewing IRB's assessment of study progress should focus on overall rather than site-specific study activities and enrollment and noted that concerns about site-specific enrollment fall within the realm of the Overall PI to address, unless a lack of enrollment at certain sites adversely affects the equitable selection of subjects (e.g., when specific sites are primarily or solely responsible for enrolling certain populations).

As described below and reflected in the Working Group's recommendations, the Reviewing IRB's assessment of study progress information in a single IRB situation differs from local IRB review in terms of the need to evaluate the overall study as well as what has occurred at each study site. In the case of participant withdrawals, the guidance provides some insight into the level of information a Reviewing IRB should collect. Per the guidance evaluating participant withdrawals can shed light on problems related to the conduct of the research, suggesting that a high rate of withdrawal could indicate the risks of the research may be greater than expected. A high rate of withdrawals also could suggest a problem with a study team's performance, which is why the guidance states that a Reviewing IRB should collect the reason for participants' withdrawal. For example, if a site reports more unanticipated problems, protocol deviations, or subject complaints than others, is that because of a higher occurrence rate at that site due to study team performance issues, because the site is more diligent in their reporting, or because more participants were enrolled at that site? The Reviewing IRB needs to obtain sufficient information to distinguish between these situations so that it can determine any appropriate follow-up action.

IMPLEMENTING OHRP AND FDA CONTINUING REVIEW GUIDANCE FOR SINGLE IRB REVIEW

When a single IRB reliance arrangement is in place, the guidance becomes less clear in terms of what information will be provided to the Reviewing IRB and who provides it. For example, does the Reviewing IRB need the brief project summary to describe only the study progress as a whole, or is it critical for the summary to capture what has occurred at each participating site? Who provides this information to the IRB – is it the study sponsor (if one exists), the Overall PI, each participating site, or a combination of these parties? A single IRB arrangement also raises questions regarding who is responsible for collecting and providing any new and relevant information to the Reviewing IRB and whether this responsibility differs for studies with and without a sponsor. For studies with a formal sponsor, the sponsor may be the entity responsible for identifying new information (including about risks), tracking studywide events (unanticipated problems, subject withdrawals), and identifying updates to informed consent documents, protocols, and applicable Investigator's Brochures. For investigator-initiated research, the responsibility for tracking this information, interpreting it, and presenting it to the Reviewing IRB usually lies with the Overall PI or lead study team. Table 2 details the Working Group's recommendations regarding each category of information the guidance recommends Reviewing IRBs collect, including who should provide the information to the Reviewing IRB and what specific information should be provided.

The considerations of the single Reviewing IRB differ from those in multi-IRB situations because the Reviewing IRB must evaluate events and other information both as they affect the overall study as well as their impact on each

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participating site. For example, the Reviewing IRB assumes responsibility for assessing how an event that occurs at one site affects that site as well as the entire study, including what site-specific versus studywide actions may be necessary (e.g., suspending research activities at a particular site versus the entire study). Some situations that may arise during continuing review where it may be clear that the Reviewing IRB likely needs to take site-specific actions (e.g., suspension or expiration of research approval for that site) include:

1) An event(s) identified at a particular site, which does not involve subjects or investigators at other sites, that suggests either a) increased risks to subjects at that site or b) that the study team is not complying with IRB determinations, the study protocol, or regulations
2) A site fails to provide information for the continuing review progress report

To make these assessments, the Reviewing IRB must have mechanisms in place to be able to identify site-specific versus study-wide issues, which likely involves working with the Overall PI and lead study team to ensure that the appropriate information will be tracked to facilitate these evaluations.

Many institutions use continuing review performed by their local IRB as an efficient means to monitor compliance, as suggested by the guidance. When using an external IRB, however, institutions may need to identify processes other than IRB review to meet their obligations for ensuring compliance, a responsibility they retain in an IRB reliance arrangement. As a result of increased use of external IRBs and elimination of continuing review for some studies, some institutions use a continuing review proxy, such as an annual check in, to track their research portfolio, study closure, and key events (e.g., serious and continuing noncompliance or unanticipated problems) that occur in ceded research. In addition, reliance agreements, like the SMART IRB Agreement, require institutions to monitor for any changes that could trigger local context issues (e.g., new conflicts of interest for study personnel, state law issues, ancillary reviews) for a ceded study. Institutions vary in whether they conduct a check in and, if they do, some consist solely of reminders to investigators (e.g., about the need to report certain events locally or to close their studies) whereas others include a more substantive collection and analysis of information from study teams.

Most aspects of assessing the adequacy of the informed consent process would not be expected to differ in a single IRB versus local IRB review situation. For example, single IRB review should not affect the Reviewing IRB's verification that the informed consent document contains the most accurate, up-to-date information about the research and the required elements of informed consent. Such verification might become more complicated in a single IRB review situation, however, if the Reviewing IRB allowed significant variation across sites in the content and format of their informed consent documents. In contrast, the expectation within the guidance for Reviewing IRBs to request the latest version of the IRB-approved protocol and sample informed consent document(s) becomes complicated in a single IRB situation because it begs the question as to whether the IRB must collect copies from each site, or at least ensure the Overall PI has a process to ensure that each site is using the appropriate version(s) of the consent form.

WORKING GROUP RECOMMENDATIONS FOR CONTINUING REVIEW

The Working Group's recommendations for the information that should be collected, provided, and evaluated as part of continuing review are presented in terms of responsibilities assumed by an Overall PI, Relying Site PI, Reviewing IRB, and Relying Institution. As described in the background section of this document, the transition to single IRB in many cases increases the responsibility for study teams, particularly for the Overall PI.

Table 2 in this section maps the Working Group recommendations to the OHRP and FDA guidance regarding continuing review and identifies the expected source of the information, who would provide the information to

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the Reviewing IRB, and the specific information that should be provided. Figure 1 illustrates the expected information flow in a single IRB situation.

Overall PI Responsibilities

- Setting up information collection expectations and processes for all participating sites, which includes:
    - Identifying studywide information that will be collected and maintained centrally and communicating these requirements to participating study teams prior to study initiation
    - Maintaining studywide data or delegating this responsibility to a designee (e.g., a coordinating center) to manage and maintain studywide data
    - Identifying how and when participating site study teams provide their information for central data storage
    - Collecting information
        - In sufficient detail to meet the Reviewing IRB's reporting requirements for continuing review
        - About site PI status, qualifications, and resources to conduct the study and site study team conflicts of interest (COIs) that could affect the study
        - About safety monitoring
        - About auditing and monitoring from all sites to identify items that may need to be reported to the Reviewing IRB
        - To be able to attest to the Reviewing IRB that:
            - None of the participating investigators' situations or qualifications have changed in ways that would adversely affect their participation in the study
            - No changes have occurred in the acceptability of the proposed research for each of the participating sites in terms of institutional commitments and applicable regulations, state and local law, or standards of professional conduct or practice
            - No changes have occurred in the COI status or management plans for personnel who have been added to or removed from the study
- Identifying and assessing whether any new and relevant information, published or unpublished, has arisen since the last IRB review, especially information about risks associated with the research. When a research study has a sponsor, the sponsor may provide studywide information either directly to the Reviewing IRB or to an Overall PI, depending on the IRB's processes. In the case of research without a sponsor, the Overall PI should be responsible for this activity, but may wish to obtain input from other participating investigators to ensure as complete and accurate an assessment of study risks and monitoring as possible.
- Monitoring study progress and conduct, site information provided, and auditing and monitoring and other reports received to:
    - Ensure study data are being provided to the designated entity in a timely manner and are of sufficient quality and completeness based on the reporting requirements of the Reviewing IRB
    - Ensure adherence with applicable data monitoring plans approved by the Reviewing IRB
    - Assess safety monitoring information to promptly address any issues identified
    - Assess adverse events and other information (e.g., protocol deviations) to identify potential changes in risks to subjects based on the frequency or severity of the events
    - Identify and communicate to the Reviewing IRB any data reporting or other issues that could affect study progress
    - Assess whether reports contain information that may need to be reported to the Reviewing IRB or that require other action (e.g., halting enrollment at a site, investigation of a site deviation, corrective action plan)
    - Ensure the plan the Reviewing IRB approved for equitable subject selection (e.g., number of subjects as well as subject demographics) is being followed
- Providing information to the Reviewing IRB at the time of continuing review about the study's progress and conduct, which should include:

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- Categorizing the enrollment status of the overall study, at minimum as
    a) Some or all sites have ongoing participant enrollment;
    b) Enrollment is complete, but study interventions are ongoing;
    c) Study activities are limited to long-term follow-up of participants at some or all sites; or
    d) Enrollment is closed, study interventions are complete, and study activities are limited to data analysis
- Overall enrollment of the study, including for each site
- Number of subject withdrawals and the reasons for withdrawal
- Notable subject experiences (e.g., complaints that could not be resolved by the study team, unanticipated problems)
- Any delays in study activities
- Expected activities for the upcoming year (e.g., subject enrollment continuation or completion of enrollment; enrollment suspension for data analysis; analysis of biospecimens)
- Any new information, published or unpublished, that could affect the study, particularly research risks, benefits, alternatives to participation, or informed consent documents

Relying Site PI Responsibilities

- Providing information to the Overall PI (or designee) for the purposes of continuing review, including:
    - The number of withdrawals and the reason for these withdrawals
    - A description of subject complaints that could not be resolved by their study team or their home institution
    - The status of each enrolled subject (e.g., active, in follow up, completed, withdrawn)
    - Study data in a timely manner
    - Attestation to the Overall PI that
        - All events that the Reviewing IRB requires to be reported have been submitted to the Overall PI previously
        - No material changes have been made at that site without prior IRB approval unless to avoid an apparent immediate hazard to subjects
        - Any changes in their situation and qualifications would not adversely affect their participation in the study
        - There are no changes in the acceptability of the proposed research in terms of their institution's commitments and applicable regulations, state and local law, or standards of professional conduct or practice
        - There have been no changes in the COI status or management plans for personnel added to or removed from the study at that site
        There are no updates to funding at that site

Reviewing IRB Responsibilities

- Informing the Overall PI of their requirements for continuing review submissions, including when reports should be submitted, content of reports, and who should communicate the information to the Reviewing IRB[3]
- Determining the appropriate expiration date for the overall study and assigning the same expiration date for all sites regardless of when the individual sites obtain IRB approval
- Collecting and reviewing sufficient information to ensure the criteria for IRB approval continue to be satisfied, including:

[3] Reviewing IRBs can be flexible in the format of continuing review reports. For example, if an annual progress report for a federal grant contains all of the information required for continuing review, that data would not need to be transferred to a new format.

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  - Study status, to identify when a study may qualify for an expedited continuing review or be excused from continuing review
  - Information about studywide progress
  - Data safety monitoring reports or safety monitoring information, to ensure the approved safety monitoring plan is being followed and that any designated DSMB/DMC has determined the research is appropriate to continue or that the review conducted as part of the IRB-approved data monitoring plan has not uncovered any concerns[4]
  - A summary of any new and relevant information, published or unpublished, that has arisen since the last IRB review (i.e., initial review or the prior continuing review, whichever was more recent)
  - Overall enrollment of the study including withdrawals and reasons for them
- When informed consent is required for a study, confirming that all study teams are using the most recently approved version(s) of the informed consent document(s), which can be achieved by the Reviewing IRB having study teams confirm within an electronic submission system which consent documents are being used, requesting copies of the most recent consent forms each site has used with subject information redacted, or obtaining an attestation from the Overall PI (or designee, such as a coordinating center) that all sites are using the most current version(s)
- Ensuring that any new and relevant information provided at continuing review is reflected in applicable informed consent document(s), requesting revisions to informed consent documents as needed and, if changes to consent document are necessary, determining which subjects must informed of the new information
- Obtaining an attestation from the Overall PI at continuing review that:
  - All events the Reviewing IRB requires to be reported have been submitted previously
  - No material changes have been made without prior IRB approval unless to avoid an apparent immediate hazard to subjects
  - None of the participating investigators' situations or qualifications have changed such that the change would adversely affect their participation in the study
  - There are no changes in the acceptability of the proposed research for each of the participating sites in terms of institutional commitments and applicable regulations, state and local law, or standards of professional conduct or practice
  - No changes in COI status or management plans have occurred for personnel added to or removed from the study
  - There are no updates to funding (which can affect the regulations applied to a study)

Relying Institution Responsibilities

- Ensuring their study teams comply with Reviewing IRB requirements for continuing review

[4] Because the IRB approves a safety monitoring plan at the initial review that they think is appropriate given the study risks and design and can conduct the continuing review with the assumption that the study continues to meet the criteria for approval, the IRB does not need to request a list of adverse events or unanticipated problems at the time of continuing review.

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Figure 1.

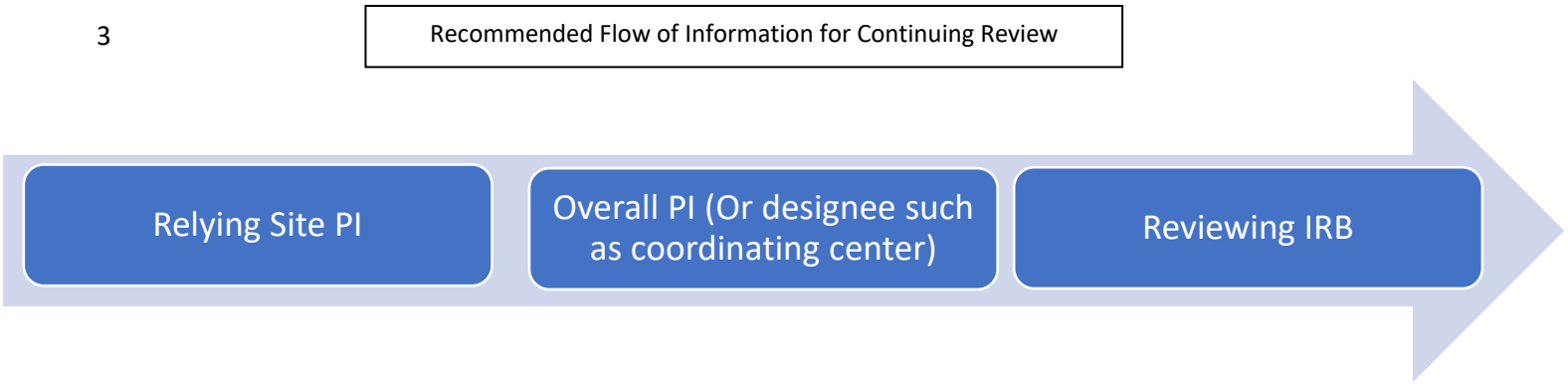

Table 2. Working Group Recommendations for Continuing Review Content, Based on OHRP/FDA Guidance

OHRP/FDA Suggested Component	Source	Who Provides Information to the Reviewing IRB*	What Information Should be Provided to the Reviewing IRB

Brief project summary: study status	Study sponsor (if one exists), applicable coordinating centers, and relying site investigators	Overall PI	The summary should identify the status of the overall study during the approval period and include
			• Enrollment status of the overall study, including whether
			  ○ Some sites or all sites have ongoing participant enrollment;
			  ○ Enrollment is complete, but study interventions are ongoing;
			  ○ Activities are limited to long-term follow-up of participants at some or all sites; or
			  ○ Enrollment is closed, study interventions are complete, and study activities are limited to data analysis
			• Notable subject experiences (e.g., complaints that could not be resolved by the study team, unanticipated problems)
			• Any delays in study activities
			• Expected activities for the upcoming year

The number of subjects accrued	Relying site investigators	Overall PI	The number of subjects enrolled and status of each subject by site.

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A brief summary of any amendments to the research approved by the IRB since the IRB's initial review or the last continuing review	IRB records or studywide records held by the Overall PI (or designee)	Overall PI	If IRB records already include a brief summary of amendments approved since the initial review or last continuing review, the IRB does not need to request this as part of the continuing review. If such a summary is needed, the Overall PI should provide it.
Any new and relevant information, published or unpublished, since the last IRB review, especially information about risks associated with the research	Study sponsor (if one exists), applicable coordinating centers, and relying site investigators	Overall PI	A summary of new and relevant information, published or unpublished, since the last IRB review (initial or continuing review, whichever was most recent) that includes a synopsis from the Overall PI of the relevance of this information to the study's risks, benefits, alternatives, and applicable informed consent documents.
A summary of both any unanticipated problems and available information regarding adverse events	Study sponsor (if one exists), applicable coordinating centers, and relying site investigators	Overall PI	Generally, IRBs do not request the submission of adverse events unless they constitute unanticipated problems. A summary of unanticipated problems and safety monitoring information that includes an analysis by the Overall PI of the unanticipated problems and adverse events, explaining whether the events have occurred at a higher rate or were more severe than previously expected or should be recategorized in terms of their relationship to any study procedures (e.g., previously thought to be unrelated but now viewed as related to a research intervention).
A summary of any withdrawal of subjects from the research since the last IRB review, and the reasons for withdrawal, if known	Relying site PI	Overall PI	The number and reasons for subjects withdrawal at each site. This information would include, for example, how many subjects withdrew their consent to participate and why, as well as how many were withdrawn by study investigators (or others) due to safety concerns or compliance issues.
A summary of any complaints about the research from subjects or others	Relying site PI	Overall PI	A summary of any complaints at each site that were unable to be resolved by the study team (or their institutions).

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OHRP/FDA Suggested Component	Source	Who Provides Information to the Reviewing IRB*	What Information Should be Provided to the Reviewing IRB
since the last IRB review			
The latest version of the IRB-approved protocol and sample informed consent document(s)	IRB electronic submission system or Overall PI	Overall PI if requested	Reviewing IRBs can meet this expectation by using their electronic submission system (e.g., asking the Overall PI to confirm which consent documents will continue to be used for each site), requesting copies of the most recent consent forms each site has used with subject information redacted, or obtaining an attestation from the Overall PI that all sites are using the most current version(s).
Any proposed modifications to the informed consent document or protocol	*Not applicable*	*Not applicable*	*This is outside of the scope for this guidance.*
For FDA-regulated research, the current Investigator's Brochure (IB), if available, including any modifications	Study sponsor (if one exists), applicable coordinating centers, or Overall PI	Overall PI	The most recent IB, if not previously provided, with an assessment of any effects on the study's risks, benefits, alternatives, or consent documents.
Any other significant information related to subject risk, such as the most recent report from any data safety and monitoring board (DSMB) or data monitoring committee (DMC) monitoring the research, if available	Study sponsor (if one exists), applicable coordinating centers, Relying Site PIs, or Overall PI	Overall PI	• Data safety monitoring reports or safety monitoring information either formal or informal to ensure the approved safety monitoring plan is being followed, that either the formal DSMB has determined the research is appropriate to continue based on their review, or that the informal review has not uncovered any additional study concerns. • A summary of any new and relevant information, published or unpublished, that has arisen since the last IRB review and synopsis from the Overall PI of the relevance of this information to the study's risks, benefits, alternatives, and applicable informed consent documents.

1 * In some cases, an IRB may allow a designee of the Overall PI, such as a coordinating center, to provide the
2 information to the Reviewing IRB.

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