

Focus On: Continuing Review

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Topics

- Why does the IRB conduct continuing review (CR)
- What constitutes meaningful and substantive CR
- CR by the Convened IRB vs. Expedited Review
- Applying Expedited Review categories 8 and 9
- Lapses in IRB approval
- Continuing Review and the Revised Common Rule



Why does the IRB conduct Continuing Review?

Why Does the IRB Conduct Continuing Review?


- The Common Rule requires it
 - 38 CFR 16.109(e): “An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year...”
 - Monitoring mechanism that assures that continued safeguards are in place to protect the rights and welfare of study participants

Poll: When do you send out CR reminders

- When do you send out the first continuing review reminder:
 - 3 months or more before approval expires
 - 2 months before approval expires
 - 1 month before approval expires
 - 2 weeks before approval expires
 - No reminders sent

How Often Must Continuing Review be Conducted

- 38 CFR 16.103(b)(4)(ii): IRB must have written policies for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB reviews.



Substantive and Meaningful Continuing Review

What Constitutes Meaningful and Substantive Continuing Review

- All approval criteria continue to be met
 - Primary focus on whether risks continue to be minimized
 - The risks to subjects are reasonable in relation to anticipated benefits
 - The safeguards in place at the time of the original approval are, in fact, adequate to ensure the safety of subjects
- Informed consent is accurate and complete
- Informed consent form, HIPAA authorization and protocol are consistent
- Significant new findings that may affect the subject's willingness to continue participation are provided to subjects

Investigator Submits Protocol Summary & Written Status Report

- Brief summary of the research methodology
- ✓ Number of subjects accrued and withdrawn (including the reason) for the review period and since inception
- ✓ Summary of complaints regarding the research since the last IRB review
- Latest version of the IRB-approved protocol
- Current Investigator's Brochure (if applicable)

Investigator Submits Protocol Summary & Written Status Report


- ✓ Copy of the current informed consent form(s) and any new proposed informed consent form(s) along with a description of changes in the new form
- ✓ Current HIPAA authorization
- List of all amendments since last IRB approval
- ✓ Information that may impact on the risk benefit ratio, such as SAEs and complaints regarding the research

Investigator Submits Protocol Summary & Written Status Report

- ✓ Summaries, recommendations, or minutes of the Data Monitoring Committee (DMC) meetings (if applicable) or findings based on information collected by the data and safety monitoring plan
- Assurance that all identified unanticipated internal or local SAEs, have been reported as required to the IRB of record
- Summary of all unanticipated problems involving risks to subjects or others, and all internal or local SAEs

Investigator Submits Protocol Summary & Written Status Report

- ✓ Research findings to date, if available
- ✓ Relevant multi-center trial reports
- ✓ New scientific findings in the literature, or other relevant findings, that may impact on the research



Convened IRB vs. Expedited Continuing Review

How is Continuing Review Conducted?

- Convened IRB Review
- Expedited Review

Convened IRB Review: What Needs to be Reviewed and by Whom

OHRP Recommends the following

- At a minimum, all IRB members should receive and review a protocol summary and status report on the progress of the research
- At least one voting member of the IRB (e.g. a primary reviewer) needs to receive a copy of the complete protocol, including any modifications previously approved by the IRB
- All IRB members have access to the complete IRB protocol file and relevant IRB minutes

Continuing Review by Convened IRB Review: What Determinations Can be Made

- Approve
- Approve with minor modifications
- Defer approval
 - Substantive conditions = defer approval
- Disapprove

When can Continuing Review Occur by Expedited Review

- Minimal risk studies originally approved and still qualifying for expedited review categories 1-7
- Studies eligible for expedited review categories 8 or 9 at the time of continuing review

Who can Perform Continuing Review by Expedited Review

- Conducted by the IRB Chair or an experienced IRB voting member designated by the Chair
- Expedited reviewer should receive and review all documentation and complete protocol

Expedited Review: What Determinations Can be Made

- Approve
- Approve with modifications
- Defer to the convened board

Important Considerations for Determining Approval Period

SOPs need to specify

- How IRB determines effective date of initial approval
- How continuing review period will be calculated
 - 1 year approval from Oct 1, 2017 – Oct 1, 2018
 - 1 year approval from Oct 1, 2017 – Sept 30, 2018
- Whether IRB will maintain anniversary date of approval using the 30 day rule
- How IRB will communicate the date and period of approval to the Investigator

Establishing Effective Date of Initial Approval and Dates of Continuing Review: Convened IRB Issues Straight Approval

Convened IRB issues straight approval (no changes required)

- Effective date of initial approval = date of IRB meeting
- 1st Continuing Review must occur latest one year post meeting date

Example

- Convened IRB issues straight approval on April 16, 2018
- 1st Continuing Review must occur latest April 16, 2019

Establishing Effective Date of Initial Approval and Dates of Continuing Review: Convened IRB Issues Approval with Minor Mods

Convened IRB issues approval with minor mods

- Effective date of initial approval = date of confirmation that all modifications have been made
- 1st Continuing Review must occur *latest* date all modifications have been confirmed

Example

- Convened IRB issues approval with minor mods on April 16, 2018
- Revisions submitted and reviewed on April 30, 2018. Reviewer verifies that all required modifications have been made.
- 1st Continuing Review must occur latest April 30, 2019

Case Study 1: Continuing Review Expiration Date

- A protocol undergoes its initial review by the convened IRB on April 10th 2018
- The IRB approves it with minor mods for a one year period and designates an IRB member to verify that the changes have been made
- On April 20th 2018, the Investigator submits a response addressing the mods which is reviewed by the reviewer on April 24th, 2018
- What is the latest date the Continuing review must occur by?

Poll: Case Study 1

Continuing Review for the study must occur by:

- a) April 10, 2019
- b) April 20, 2019
- c) April 24, 2019
- d) Either a or c
- e) None of the above

Convened IRB Review: Establishing Continuing Review Renewal Dates after Initial Approval

- Approval and Approval with Minor Mods
 - Continuing review renewal date is set as the date of the meeting at which either of these two determinations is made, not the date that the conditions are verified (caveat is the 30-day rule)
- Defer Approval
 - Continuing review renewal date is set as the date of the meeting at which the protocol is finally approved or approved with minor mods

30 Day Rule

- When continuing review occurs annually and the IRB performs continuing review up to 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the subsequent continuing review must occur.

Expedited Review: Establishing Continuing Review Approval Date

- Approve
 - Continuing review approval date is set as the date the expedited reviewer completes his/her review
- Approve with modifications
 - Continuing review approval date is set as the date the expedited reviewer determines that the investigator has adequately addressed all required modifications requested
- Defer approval to convened IRB
 - Refer to convened board requirements

Expedited Review: Establishing Continuing Review Renewal Date

- Renewal date/Continuing review expiration date must occur no later than one year after the last approval (caveat is the 30-day rule)
 - Last approval granted on January 15, 2018
 - Continuing Review Approval must occur latest January 15, 2019

Case Study 2: Continuing Review Expiration Date

- A protocol expiring on January 15, 2018 is submitted for continuing review
- The study continues to qualify for expedited review
- On December 10, 2017 the expedited reviewer reviews the study and requests a number of clarifications from the investigator
- The investigator submits the requested information and on December 29, 2017, the expedited reviewer confirms that all issues have been addressed and the study is approved for another one year period

Poll: Case Study 2

The next expiration date for the study should be:

- a) December 10, 2018
- b) December 29, 2018
- c) January 15, 2019
- d) Either b or c
- e) None of the above



Expedited Review Categories 8 and 9

Expedited Review Category 8

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

- (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
- (b) where no subjects have been enrolled and no additional risks have been identified; or
- (c) where the remaining research activities are limited to data analysis

Expedited Review Category 9

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

Case Study 3: Continuing Review by Expedited Review

- A research study is evaluating cytokine levels in subjects diagnosed with Rheumatoid Arthritis.
- 50 subjects will be enrolled per year over the next five years.
- 20ml of blood will be collected by venipuncture 4 times per week for 6 weeks.
- The research study is not conducted under an IND or IDE
- The meeting minutes from the initial approval note that the study was deemed no greater than minimal risk
- No additional risks have been identified during the approval period

Poll: Case Study 3

- At continuing review, the study is eligible for review by
 - a) The Convened IRB
 - b) Expedited Review Category 2
 - c) Expedited Review Category 8
 - d) Expedited Review Category 9

Case Study 4: Expedited Review

- A research study is evaluating the effects of urban pollution on pulmonary status in healthy adults
- Subjects will undergo the following:
 - Monthly surveys regarding exercise and pulmonary symptoms and
 - A single chest x-ray 5 years after enrollment
- The study was initially reviewed by the convened IRB and the meeting minutes indicate that the study involves no greater than minimal risk

Poll: Case Study 4

- At the time of the continuing review, the study is eligible for review by
 - a) The convened IRB
 - b) Expedited Review Category 4
 - c) Expedited Review Category 8
 - d) Expedited Review Category 9
 - e) Additional information is needed



Lapses in IRB Approval

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- If Approval Expires:
 - Local research office must promptly notify the investigator
 - Investigator must stop all research activities including, but not limited to
 - Enrollment of new subjects
 - Continuation of research interventions or interactions with currently participating subjects
 - Data analysis

Lapses in IRB Approval

- Investigator must immediately submit to the IRB Chair a list of research subjects who could be harmed by stopping study procedures
- IRB Chair, with appropriate consultation with the Chief of Staff, determines if subjects on the list may continue participating in the research interventions or interactions

Lapses in IRB Approval

- Once study approval has expired, IRB re-review and re-approval must occur before the study can resume
- The IRB cannot retrospectively grant approval to cover a period of lapsed IRB approval



Continuing Review and The Revised Common Rule

Continuing Review and the Revised Common Rule: What Has Not Changed

- IRBs must continue to follow written procedures for conducting initial and continuing review of research and reporting its findings and actions to the investigator and institution
- IRBs must continue to determine 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 the previous review

Continuing Review and the Revised Common Rule: What Has Changed

- IRBs shall conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk, but not less than once per year, except in the following cases:
 - Research eligible for expedited review
 - Research that has progressed to a certain point
 - Research reviewed by the IRB in accordance with the Limited IRB Review provisions (certain research eligible for exempt review)
- IRBs must document the rationale for conducting continuing review of research that does not require CR

Elimination of Continuing Review in the following cases

- Research that initially qualified for Expedited Review
- Research that has progressed to the point that it involves only one or both of the following:
 - Data analysis, inclusive of analysis of identifiable private information or identifiable specimens, and/or
 - Access to follow-up clinical data obtained from procedures that subjects undergo as part of clinical care

Elimination of Continuing Review in the following cases (continued)

Research reviewed by the IRB using limited IRB review

- Applies to 4 specific categories of Exempt Research
- IRB does not have to ensure that all of the 111 approval criteria are met
- IRB review is limited to (1) determining that adequate provisions to protect the privacy of subjects and maintain the confidentiality of their data exist and/or (2) Broad consent is appropriately obtained and documented (or waiver of documentation is appropriate)

Exempt Research Requiring Limited IRB Review: 38 CFR 104d(a)(2)(iii) and 104d(a)(3)(i)(c)

- Research involving educational tests, surveys, interviews, or observation of public behavior if the information obtained is recorded such that the identity of human subjects can be readily ascertained and the IRB conducts a limited IRB review to ensure that adequate provisions exist to protect the privacy of subjects and maintain the confidentiality of their data (38 CFR 104d(a)(2)(iii))
- Research involving benign behavioral interventions when identifiable information is collected from an adult through verbal, written, or audiovisual recordings and the subject prospectively agrees to both the intervention and data collection and the IRB conducts a limited IRB review to ensure that adequate provisions exist to protect the privacy of subjects and maintain the confidentiality of their data (38 CFR 104d(a)(3)(i)(C))

Exempt Research Requiring Limited IRB Review: 38 CFR 104(d)(7)

- Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research if the IRB conducts a limited IRB review and determines that broad consent is appropriately obtained and documented (or waiver of documentation is appropriate) and adequate provisions exist to protect the privacy of subjects and the confidentiality of their data (38 CFR 104(d)(7)).

Exempt Research Requiring Limited IRB Review: 38 CFR 104(d)(8)

- Research involving the use of identifiable private information or identifiable biospecimens for secondary research if (i) broad consent was appropriately obtained; (ii) documented (or documentation is waived if appropriate); (iii) the IRB conducts a limited IRB review and determines that adequate provisions exist to protect the privacy of subjects and maintain the confidentiality of their data and the research to be conducted is within the scope of the broad consent; and (iv) there are no plans to return individual research results to subjects (38 CFR 104(d)(8)).

References

- Federal Policy for the Protection of Human Subjects ('Common Rule'): 38 CFR Part 16 (Dept of Veterans Affairs)
- Department of Veterans Affairs, Veterans Health Administration handbooks:
 - VHA Handbook 1200.05, Requirements for the Protection of Human Subjects Research (https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=3052)
 - ORD FAQ on Informed Consent Forms – Expiration Dates (<http://vaww.research.va.gov/resources/policies/guidance/Informed-Consent-Forms-Expiration.pdf>)
 - ORD Guidance on Continuing Reviews (<https://www.research.va.gov/resources/policies/guidance/ContinuingReview.pdf>)
- Office of Human Research Protections (OHRP), Department of Health and Human Services (HHS):
 - Guidance on IRB Continuing Review of Research (<http://www.hhs.gov/ohrp/policy/continuingreview2010.html>)
 - Categories of Research That May Be Reviewed by the IRB through an Expedited Procedure (<http://www.hhs.gov/ohrp/policy/expedited98.html>)
 - Determination Letter to Howard University, May 7, 2015 (<https://www.hhs.gov/ohrp/compliance-and-reporting/determination-letters/2015/may-7-2015-howard-university/index.html>)
 - Determination Letter to University of Washington, April 21, 2014 (<https://www.hhs.gov/ohrp/compliance-and-reporting/determination-letters/2014/april-21-2014-university-of-washington/index.html>)
 - Determination Letter to University of Washington, December 17, 2012 (http://wavback.archive-it.org/4657/20150826185104/http://www.hhs.gov/ohrp/detrm_lettrs/YR12/de)

Contacts

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Questions?

Office for Human Research Protections (OHRP) - Categories of Research

Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure¹

Applicability

- A. Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
- B. The categories in this list apply regardless of the age of subjects, except as noted.
- C. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects= financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- D. The expedited review procedure may not be used for classified research involving human subjects.
- E. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.
- F. Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

- 1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
 - a. (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - b. Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- 2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - a. (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

- b. from other adults and children², considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. [45 CFR 46.101\(b\)\(4\)](#). This listing refers only to research that is not exempt.)

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

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. [45 CFR 46.101\(b\)\(2\)](#) and (b)(3). This listing refers only to research that is not exempt.)

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

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

- b. where no subjects have been enrolled and no additional risks have been identified; or

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

¹ An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in [45 CFR 46.110](#).

² Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." [45 CFR 46.402\(a\)](#).

Source: [63 FR 60364-60367](#), November 9, 1998.