Overview

For any non-exempt human research study where continuing review and approval has not occurred by the end of its approval period, the study is automatically considered expired. If study approval expires, all research-related activities for the study must stop except if a determination is made that the health or welfare of a participant, or participants, will be jeopardized if a study intervention or other research activity is discontinued.

When the study approval expires, no research funds supporting the engaged human subject research activities of the study (e.g., recruitment and enrollment activities, data collection or data analysis) may be incurred unless it is determined to be in the best interests of already enrolled subjects to continue participating in the research. For example, “when the research interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects.”


1 FDA Guidance (2012):

FDA expects that IRB procedures will be followed by investigators such that lapses of IRB approval will be a rare occurrence. However, temporarily continuing participation of already enrolled subjects in a research project during the period when IRB approval has lapsed may be necessary or appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects (e.g., investigational chemotherapy regimen in an oncology trial), or when withholding those interventions poses increased risk to the subjects. If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research protocol, data collection (especially safety information) should also continue for such subjects (e.g., implantable device requiring long-term follow-up). If the investigator is initially determining whether it is in the best interests of already enrolled subjects to continue to participate in the research after IRB approval has expired, the investigator should consult the treating physician (if the investigator is not the treating physician). This determination may be made for all enrolled subjects as a group or for individual subjects.

For studies involving an exception from informed consent for emergency research conducted under 21 CFR 50.24, an IRB must notify both the clinical investigator and the sponsor in writing of the IRB’s determination that it cannot approve a study (21 CFR 50.24(e) and 56.109(e)). See, for example, 21 CFR 56.103(a) (studies that must meet requirements for prior submission in parts 312, 812, and 813 “shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part”); 21 CFR 812.110 (a) (investigator shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval); 21 CFR 312.66 (requiring investigators to assure that study is subject to continuing review by an IRB meeting the requirements of part 56). 25 See 21 CFR 56.102(g). In all cases, investigator should verify that the IRB agrees with this determination as soon as possible.

OHRP Guidance (2010):

The HHS regulations at 45 CFR part 46 make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. A lapse in IRB approval of research occurs whenever an investigator has failed to provide continuing review information to the IRB or the IRB has not conducted
research study generally no later than thirty (30) business days after the expiration date if the Principal Investigator (PI) fails to request that the expired study be re-activated and to submit a request for re-approval.

In the event of an administrative closure due to study expiration, the HRPP will notify the PI (and the Office for Sponsored Projects (OSP) for sponsored research) regarding the closure as described in this procedure to assist in preventing any spending on a study with active funding. The HRPP Director and other designated HRPP staff also will be notified of all expired protocols regardless of whether the study is sponsored as specified below.

If the IRB approval of a research study expires due to the PI’s failure to submit a continuing review or study closure request and/or if a PI has a pattern of allowing studies to expire without submitting a continuing review or closure request, the IRB may consider whether such a pattern represents serious and/or continuing noncompliance in accordance with Policy 700: Noncompliance (See https://your.yale.edu/research-support/human-research/policies-procedures). Examples of continuing noncompliance may include repeated or deliberate failure of a PI to submit the continuing review request in a timely manner (i.e., sufficiently in advance of the expiration date for the IRB to review and approve).

Preventative Measures

The PI is responsible for ensuring that all human research protocols for which he or she maintains oversight are reviewed by the IRB on an annual basis unless a review period of less than one year is specified except for certain types of non-exempt studies which are granted a two-year approval period. See, 100 GD.2, IRB Approval and Expiration Dates.

The PI is sent several system-generated notifications regarding a pending expiration of IRB approval, as well as a notification once the IRB approval of his/her research study has expired. These notifications also serve to remind the PI that all human research-related activities must stop unless continuation of a research activity is in the best interest of the currently enrolled participant(s). The notification further informs the PI to contact the IRB immediately if he/she believes that the research intervention(s) hold out the prospect of direct benefit to the subjects or if the health or welfare of a participant, or participants, will be jeopardized if a study intervention is discontinued. If the PI believes it is in the best interest of a subject to continue research activities during the lapse, a request to continue the subject should be submitted to the IRB using the 100 FR 22, Yale IRB Protocol Exception form (See https://your.yale.edu/research-support/human-research/forms-templates). Based on the information provided by the PI on the Protocol Exception form, an IRB Chair may agree with the PI to allow research interventions and interactions to continue for one or more research participants. Such a decision will be communicated via email to the PI.

In addition to the notifications from the e-IRB system, approval letters to PIs include information to remind them that they are responsible for ensuring that a submission for continuing review or closure is made to the applicable IRB within a specified timeframe prior to the expiration date to prevent a lapse in IRB approval.

PIs and protocol correspondents (if named) are sent automated email reminder notices from the e-IRB system prior to the expiration of the approval period. At approximately 30 days prior to expiration of the IRB approval, designated HRPP staff continuing review and re-approved the research – with or without conditions – by the expiration date of IRB approval. In such circumstances, all research activities involving human subjects must stop after IRB approval expired, unless it is determined to be in the best interests of already enrolled subjects to continue participating in the research. Enrollment of new subjects cannot occur after the expiration of IRB approval. Continuing participation of already enrolled subjects in a research project during the period when IRB approval has lapsed may be appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects.

The determination regarding whether it is in the best interests of already enrolled subjects to continue to participate in the research after IRB approval has expired may be made initially by the investigator, possibly in consultation with the subjects’ treating physicians (if the investigator is not the subjects’ treating physician), but the investigator as soon as possible should submit a request for confirmation that the IRB agrees with this determination. The determination by the IRB may be made by the IRB chairperson, by another IRB member or group of IRB members designated by the IRB chairperson, or at a convened meeting of the IRB. Furthermore, this determination may be made for all enrolled subjects as a group or for each individual subject. If the investigator or IRB determines that it is not in the best interests of already enrolled subjects to continue to participate, investigators must stop all human subjects research activities, including intervening or interacting with subjects and obtaining or analyzing identifiable private information about human subjects (45 CFR 46.109(a) and (e)).

2 e-IRB-generated emails may route to the recipient’s Junk mailbox, so all PIs are advised to routinely check their Junk mail for these reminders.

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that support the review of the study is provided an e-IRB-generated list of investigators that have received the 30-day notification for their particular protocols.

A designated HRPP staff member will call the PI within 15 days of the protocol expiration to inquire about the status of the renewal submission.

Designated HRPP staff is responsible for monitoring the status of IRB approvals of studies on a weekly basis through the e-IRB database management software.

**Failure to obtain IRB Approval prior to the Expiration Date**

Study approval expires (and is considered lapsed) whenever a PI fails to submit continuing review information to the IRB or the IRB has not conducted continuing review and re-approved the research – with or without conditions – by the expiration date of IRB approval. If the PI has not submitted his or her protocol to the IRB and obtained continuing review approval or closure confirmation by the expiration date, the IRB approval automatically expires. The PI is notified of the expiration of IRB approval via an e-IRB-generated notification entitled *Continuing Review Deadline Passed*. The notification alerts the PI of the expiration and instructs the PI to refer to the Investigator Manual in the IRES IRB Library for detailed information on the consequences of expiration and when and how to submit a protocol exception request using the 100 FR 22, Protocol Exception Request Form if the PI believes it is in the best interest of a subject(s) to continue research activities during the lapse in approval. In the notice, the PI is also directed to contact the Office for Sponsored Projects (OSP) for sponsored studies. The notification of the expiration of IRB approval is included in the IRB study file.

The consequences of the expiration of IRB approval are as follows:

1. All research activities must stop, including recruitment, enrollment of new subjects, research interventions or interactions, data sharing/reporting, data collection and analysis of identifiable data *unless* it is determined to be in the best interests of already enrolled subjects to continue participating in the research. (For example, when the research interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects);
2. The research may continue only after the PI receives written approval from the IRB; and
3. Procedures to close the research are initiated in accordance with this procedure.

The lapse in IRB approval *for research that continues* without IRB reapproval or formal closure represents noncompliance with federal regulations and University policy and is handled in accordance with the Yale University HRPP Policy 700 (Noncompliance, Suspension and Termination). Specifically, the HRPP Regulatory, Compliance, and Quality team or designee or an IRB Chair will review the lapse and consider whether the lapse represents possible serious or continuing noncompliance. If the lapse may represent *possible* serious or continuing noncompliance, it will be referred to the applicable IRB for a final determination in accordance with 700 PR.3, IRB Review and Investigation of Reports of Noncompliance.

**Requirements for IRB approval after the Expiration Date**

A PI must submit a request for continuing review or request to close generally within thirty (30) business days after the expiration date. The *30 business day period does not constitute an extension of the IRB approval period*. The period is meant to allow for continuing review or request-to-close submissions that may be in process before procedures to close the research protocol are initiated by the IRB. Research activities must be stopped during this period, *unless* it is determined to be in the best interests of already enrolled subjects to continue participating in the research. For example, "when the research interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects. In addition, the PI must include the reason for the lapse in obtaining IRB approval, as well as future measures to prevent a reoccurrence of a lapse in approval.

**Administrative Closure**

The Yale HRPP will administratively close a study generally within thirty (30) business days after the expiration date if the PI has not submitted a continuing review or request-to-close request to the IRB.

When a study is administratively closed, a letter is sent via the e-IRB system to the PI indicating that there has been an expiration of IRB approval and the research study has been closed. The administrative closure letter is included in the IRB study file.

A sortable report of administratively closed protocols is prepared weekly by designated HRPP staff and provided to the following:
For each protocol that is closed because of expiration, the report generally will include the following, but may be modified as necessary:

- Protocol ID #
- IRES PT #
- Expiration Date
- Administrative Closure Date
- Study Status
- Study Name
- Investigator Name
- Department Name
- Study Primary Contact
- HRPP Staff Owner
- IRES PT Sponsor Type, if applicable
- IRES PT Funding Status, if applicable
- IRES IRB Funding Information
- HRPP Notes regarding any other relevant information regarding the lapse and subsequent administrative closure
- OSP Notes regarding any other relevant information regarding the lapse and subsequent administrative closure
- Whether a request to continue treatment on enrolled subjects after study expiration was approved by the IRB; and
- Any other relevant information regarding the lapse and subsequent administrative closure.

The HRPP Regulatory Analyst (HRPP RA) staff will refer to the report when an administratively closed protocol (all studies regardless of funding) is subsequently submitted late to the IRB for reapproval.

The HRPP will conduct an inquiry of the PI regarding any human subjects research activity that occurred during the lapse. The PI will be instructed to complete the form 700 CH 2, Human Investigation Committee/Human Subjects Committee Expiration in Yale IRB Approval/Administrative Closure Summary Sheet via a Qualtrics survey and request to re-open an expired study.

The OSP Director of Financial Operations and/or designated OSP staff member will be notified when the survey indicates expenditures charged to an award linked to the expired protocol.

If OSP discovers that spending occurred during a period when IRB approval has lapsed, the HRPP is notified by OSP of any reported human subjects research activity that occurred during the lapse by sending a communication to:

- HRPP Director
- HRPP Assistant Director, Regulatory, Compliance, and Quality
- HRPP Senior Manager, Operations and External Relationships
- HRPP Regulatory Analysts and other designated HRPP staff
- OSP Director of Financial Operations, and/or other designated OSP staff

This information is also recorded in the above-referenced weekly report referenced above.

If the PI has submitted a continuing review form late, but before the expiration date and/or the PI demonstrates a good faith effort in working toward obtaining IRB approval of the continuing review prior to administrative closure, the HRPP may postpone the administrative closure of the study after receiving approval by the IRB Chair or designee. The HRPP designee must ensure that documentation of the above decision by the IRB Chair or designee is filed appropriately in the study file.

Related Documents

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3 The e-IRB system, IRES-IRB, and the OSP electronic database, IRES PT, will be cross-checked for funding status.
Policy 700, Noncompliance, Suspension, and Termination

700 PR.3, IRB Review and Investigation of Reports of Noncompliance

100 GD.2, IRB Approval and Expiration Dates

100 FR 22, Protocol Exception Request Form

700 CH 2, Human Investigation Committee/Human Subjects Committee Expiration in Yale IRB Approval/Administrative Closure Summary Sheet

References


Revision History

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