

## The University of Texas MD Anderson Cancer Center Institutional Review Board Policy on Continuing Review of Research

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### SCOPE

This policy applies to all IRB approved research conducted at The University of Texas MD Anderson Cancer Center (MD Anderson).

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### PURPOSE

The purpose of this document is to provide guidance to investigators on when to submit, what to submit and how to submit a continuing review for a research protocol as per the human subjects protection and FDA regulations at 45CFR§46.109 and 21CFR§56.109.

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### REGULATIONS AND POLICY

**45CFR §46.109(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, and shall have authority to observe or have a third party observe the consent process and the research.

**21CFR §56.109(f)** An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to have a third party observe the consent process and the research.

**MDA Policy** All research protocols involving human subjects will be reviewed by the IRB within 365 days of the initial IRB approval date or last continuing review approval date. The time interval will be determined by the IRB based on the level of risk in the protocol. In addition, the IRB will review protocol treatment plans and safety information in the informed consent document and request modifications on a continuous basis throughout the year during the review of adverse events.

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### Key Considerations When Evaluating Research undergoing Continuing Review

Criteria for IRB approval of research undergoing continuing review:

In order to re-approve research at the time of continuing review, the IRB must determine that all of following requirements are satisfied:

- Risks to subjects are minimized (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes (45 CFR 46.111(a)(1));

- Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(2));
- Selection of subjects is equitable (45 CFR 46.111(a)(3));
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, and appropriately documented in accordance with, and to the extent required by, HHS regulations at 45 CFR 46.116 and 46.117, respectively (45 CFR 46.111(a)(4) and (5));
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6));
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data (45 CFR 46.111(a)(7));
- Appropriate safeguards are included to protect subjects likely to be vulnerable to coercion or undue influence (45 CFR 46.111(b)); and
- When the research involves pregnant women, fetuses, or neonates; prisoners; or children, the research satisfies the additional requirements for IRB approval under HHS regulations at subpart B, C, or D, respectively, of 45 CFR part 46.

When conducting continuing review, the IRB will ensure that the research, as previously approved, satisfies all of the above criteria. The IRB will determine if there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB's prior determinations, particularly with respect to the IRB's prior evaluation of the potential benefits or risks to the subjects. The IRB will also assess whether there is any new information that would necessitate a modification to the protocol and/or the informed consent document.

The IRB has the authority to disapprove or require modifications in (to secure re-approval of) a research activity that does not meet the above criteria (45 CFR 46.109(a)). If the research does not satisfy all of the above criteria, the IRB must require changes that would result in research satisfying these criteria, defer taking action, or disapprove the research.

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## PROCEDURE

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Principal Investigators (PIs) receive an initial continuing review notification as a reminder at 60 days prior to the protocol expiration date. The initial notification is sent via the electronic CORE system to the PI, the additional contact and the protocol manager.

PIs should ensure that the IRB can conduct a substantive review of the research during the continuing review.

The IRB requires you submit a brief summary of the protocol to date, this could be included as part of a progress report that includes the following:

- The number of subjects accrued to date
- A summary of unanticipated problems and adverse events that have occurred since the last review
- A summary of any withdrawals of subjects from the research since the last review
- Is the protocol meeting its expected rate of enrollment
- A summary of any complaints about the research since the last IRB review;
- A summary of any recent literature that may be relevant to the research and any amendments or modifications to the research since the last IRB review;

- Any other significant information related to subject risk
- Data safety monitoring reports are required to be reported to the PI so that routine monitoring reports are submitted to the IRB.

The continuing review form should be submitted to the IRB via the electronic CORE system.

Once received the continuing review form will be reviewed either by convened board or by expedited review (see below for criteria).

The continuing review may be:

- Approved: No further actions are required by the PI
- Modifications required to secure approval: Additional actions are required by the PI
- Deferred: Additional actions are required by the PI.
- Disapproved: Changes to the protocol are required to satisfy the criteria for approval. If the protocol is deferred or disapproved, the protocol will be closed to new patient entry until the IRB actions are submitted and IRB approved.

The IRB will notify the PI in writing of its decision to approve or disapprove the proposed research, or of modifications required to secure IRB approval of the research (45 CFR 46.103(b)(4) and 46.109(d)).

PIs will receive a notification via Outlook notifying them that the IRB's Continuing Review determination memo is available in CORE.

If the IRB decides to disapprove the research, it will include in its determination memo a statement with the reasons for its decision and will provide the PI an opportunity to respond in person or in writing (45 CFR 46.109(d)). The PI should respond via a generic memo in PDOL. If the disapproval requires a change to the protocol and/or ICD, the amendment should be submitted via PDOL.

If the continuing review is not received during the initial notification, the IRB sends out additional reminders at 30 days and 2 weeks prior to the protocol's expiration date. It is the PI's responsibility to ensure that the continuing review is submitted in a timely manner for IRB review.

### **Lapsed Continuing Review:**

If the continuing review is not received by the expiration date the continuing review is lapsed and the following will occur:

- Protocol is closed to new patient entry
- Enrollment of new participants must cease while protocol is lapsed
- The IRB will determine whether existing participants may continue further protocol related interventions.
- PI will be listed as non-compliant in the electronic research system, and will not be allowed to participate on a new protocol as PI, Co-PI, or Collaborator.
- The PI's Department Chair will be notified of the IRB non-compliance status

The HHS regulations at 45 CFR part 46 and MD Anderson IRB 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 a PI has failed to provide continuing review information to the IRB or the IRB has not conducted continuing review and re-approved the research – with or without contingencies – by the expiration date of IRB approval.

At 30 days past the expiration date, the following actions will occur:

- All protocols for the noncompliant PI will be closed to new patient entry (CNPE)
- The PI's Department Chair will be notified of the IRB non-compliance status

At 60 days past the expiration date, the following actions will occur:

- The IRB has the authority to suspend the protocol. The IRB will refer the suspension to the VP, Clinical Research Administration to determine if additional actions are required. The suspension will also be reported to the Division Head/Department Chair, Institutional Officials and regulatory authorities as required.
- The IRB will inform investigators where non-compliant PI is listed as Co-PI and collaborator to remove him/her from their protocol(s)
- The PI's Department Chair will be notified of the IRB non-compliance status

The protocol will remain CNPE until the continuing review form is submitted to the IRB and presented for convened board review. After IRB approval, the PI will receive the IRB determination memo and the protocol will be re-opened to new participant accrual.

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## Criteria for Expedited Review

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The IRB may use an expedited review procedure to conduct continuing review of research for the following:

Expedited Category (8)

- (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 Category (9)

- The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE);
- Expedited review categories (2) through (8) do not apply to the research;
- The IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk to the subjects; and
- No additional risks of the research have been identified

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## **Continuing Review - Modifications Required to Secure Approval**

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Protocols that have undergone continuing review and modifications are required to secure approval are given 60 days to provide a response.

If a response is not submitted and IRB approved then the following actions will occur:

At 60 days:

- Protocol will be closed to new patient entry
- PI will be listed as non-compliant in the electronic research system, and will not be allowed to participate on a new protocol as PI, Co-PI, or Collaborator.
- The PI's Department Chair will be notified of the IRB non-compliance status

At 90 days:

- All protocols for the noncompliant PI will be closed to new patient entry
- The PI's Department Chair will be notified of the IRB non-compliance status

At 120 days:

- The IRB has the authority to suspend the protocol. The IRB will refer the suspension to the VP, Clinical Research Administration to determine if additional actions are required. The suspension will also be reported to the Division Head/Department Chair, Institutional Officials and regulatory authorities as required.
- The IRB will inform investigators where non-compliant PI is listed as Co-PI and collaborator to remove him/her from their protocol(s)
- The PI's Department Chair will be notified of the IRB non-compliance status

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## **Continuing Review – CIND Protocols**

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Compassionate IND (CIND) protocols are single patient access to investigational or unusual treatment for a condition that is considered refractory to all appropriate conventional therapy and for which no approved experimental research protocol exists. This authorization is provided out of compassion for the patient's need and not as a mechanism for conducting any type of clinical research. For this reason, CIND protocols undergo continuing review more frequently than standard protocols. CIND protocols must undergo continuing review every three months. At this time, the investigator may request termination of the protocol or justify why the compassionate use treatment should continue.

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## **Continuing Review – Common Rule**

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The Office of Human Subjects Protection has put in place procedures for implementation of the Revised Common Rule – 2018 Requirements. The implementation procedures for ongoing research will be applied at three different time points dependent on which occurs first.

- During a protocol amendment submitted to the IRB
- During the normal continuing review cycle
- During protocol activation

Please refer to the *SOP for IRB Implementation of the Revised Common Rule – 2018 Requirements* for steps on transitioning ongoing research during continuing review.

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## **Additional Information**

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It is the responsibility of the department chair and division head to expediently assign a new PI to protocols if a PI has left the institution. If these protocols are not amended to reflect a new PI, then it will be the responsibility of the department chair or division head to complete the continuing review form and/or respond to any outstanding contingencies within the specified timeframe according to the above continuing review policy.

The new PI or the Division Head/Department Chair will be subject to the same actions as listed above.

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## **Administrative Check by IRB Staff**

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The following items are checked by the IRB Staff when a continuing review is submitted:

1. Check to make sure review designation (Full or expedited) is appropriate for study (Lab versus clinical, Closed to new patient entry (CNPE), Patients on active therapy, Low risk determination)
2. Check to see if PI requested CNPE or Termination.
3. Check to see if the Outside Physician Being Utilized box is checked. If so, you will need to check the Informed Consent Document (ICD) for Outside Physician's paragraph
4. Confirm accrual has not exceeded its limit
5. Confirm accrual rate if accrual appears slow
6. Check verbal translations versus translated consents

7. Confirm that the toxicity and response profile are appropriate to protocol
8. Review the ICD Risks (See SOP “Review of Informed Consents”)
9. Check protocol for Pediatric population
10. Confirm PI has provided a summary of safety events that have occurred for this CR cycle.
11. Confirm PI has provided a deviation log for this CR cycle.
12. Confirm that all attachments submitted with the CR match the protocol
13. If protocol is open to accrual, confirm that Co-PIs and Collaborators are still with the institution.
14. Check if Sponsor is Department of Defense
15. Check if Sponsor is NIH – Certificate of Confidentiality language will be required to be in the consent document – confirm that participants were informed

For laboratory studies and data reviews all the above will be checked in addition to the below items:

1. Confirm that the total number of samples/charts to date was provided
2. Check to see if registration is required and if patients are registered
3. Confirm that a summary of research was provided
4. Check to make sure study progress appropriate for time study open

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### **Additional Protections for the Inclusion of Children in Research**

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For any protocol involving children, the IRB must determine which of the four categories of research apply to that study, if any. The IRB will document the rationale for this choice. The IRB will use the Vulnerable Populations – Children checklist.

[45 CFR 46.404](#)- Research not involving greater than minimal risk to the children.

To approve this category of research, the IRB must make the following determinations:

- the research presents no greater than minimal risk to the children; and adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

**45 CFR 46.405-** Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

To approve research in this category, the IRB must make the following determinations:

- the risk is justified by the anticipated benefits to the subjects;
- the relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches; and
- adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

**45 CFR 46.406-** Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition.

In order to approve research in this category, the IRB must make the following determinations:

- the risk of the research represents a minor increase over minimal risk;
- the intervention or procedure presents experiences to the child subjects that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations;
- the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition; and
- adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

A fourth category of research requires a special level of HHS review beyond that provided by the IRB.

**45 CFR 46.407-** Research that the IRB believes does not meet the conditions of 45 CFR 46.404, 46.405, or 46.406, but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

If the IRB believes that the research does not meet the requirements of 45 CFR 46.404, 46.405, or 46.406, but finds that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, it may refer the protocol to HHS for review. The research may proceed only if the Secretary, HHS, or his or her designee, after consulting with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following an opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406, or (2) the following:

- the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- the research will be conducted in accordance with sound ethical principles; and
- adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

**Wards:** When the protocol involves children who are wards of the state the IRB considers all of the regulations of 45 CFR 46.406, 45 CFR 46.407 and 45 CFR 46.409(a) to make the appropriate finding(s).

**Additional safeguards for Children in Clinical Investigations (FDA)**

When the protocol involves children as participants, the IRB considers all of the regulations of FDA 21 CFR 50.51, FDA 21 CFR 50.52, FDA 21 CFR 50.53, FDA 21 CFR 50.54, and FDA 21 CFR 50.55 to make the appropriate finding(s) under which the children may be included.

Wards: When the protocol involves children who are wards of the state the IRB considers all of the regulations of FDA 21 CFR 50.53, FDA 21 CFR 50.54, and 21 CFR 50.56(a) to make the appropriate finding(s).

- An MD Anderson Clinical Ethicist may serve as the advocate for wards of the state when necessary.

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**REFERENCES**

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21 CFR 56.109  
 45 CFR 46.109  
 45 CFR 46.103(b)(4)  
 45 CFR 46.111  
 45 CFR 46.404, 46.405, 46.406, 46.407, 46.408, 46.409(a)  
 21 CFR 50.51, 50.52, 50.53, 50.54, 50.55, 50.56(a)

<b>Date</b>	<b>Action</b>	<b>Initials</b>	<b>Description</b>
4.19.2019	Updated	MT	Updated continuing review policy
6.25.2019	Updated	MT	Updated continuing review policy, added common rule implementation during continuing review, added CIND requirements for continuing review, added information regarding inclusion of children