Human Subject Protection Program
Investigator Guidance
November 5, 2020

CONTINUING REVIEW REQUIREMENTS AND SUBMISSION OF CLOSURE REPORTS

Overview

- For research meeting the following criteria, DHHS and FDA regulations require the IRB to continually review ongoing research at intervals appropriate to the potential risk to participants, but at least annually.

  - ☐ Research that involves more than minimal risk to subjects
  - ☐ Research that is FDA regulated:
    - o Clinical investigations of drugs or biologics
    - o Clinical investigations of devices
  - ☐ Research that involves no greater than minimal risk to subjects and was initially approved on or before January 20, 2019.

- If an Investigator does not wish to continue a research study, then a study closure or final report must be submitted in iStar.

- **NOTE:** Exempt research studies have no expiration date. However, investigators are responsible for submitting a study closure or final report when the research concludes.

Continuing Review Frequency

Studies Approved Under Pre-2018 Common Rule (on or before January 20, 2019):

- Continuing review of all non-exempt research is required at least annually. The IRB may require more frequent review depending on the level of risk.

  - ☐ Even if no changes are made,
  - ☐ Even if the only study activity is participant follow-up, and
  - ☐ Even if the only study activity is data analysis of data that are identifiable.

More than Minimal Risk Studies Approved Under the 2018 Common Rule (on or after January 21, 2019):

- Continuing review of all more than minimal risk research is required at least annually. The IRB may require more frequent review depending on the level of risk.

  - ☐ Even if no changes are made,
  - ☐ Even if the only study activity is participant follow-up, and
  - ☐ Even if the only study activity is data analysis of data that are identifiable.

Minimal Risk Studies Approved Under the 2018 Common Rule (on or after January 21, 2019):

- Minimal risk research studies reviewed and approved by the CHLA IRB that meet expedited review criteria and are not FDA regulated are approved by the CHLA with no expiration date, unless the designed IRB reviewer determines otherwise.

CHLA IRB Approval Period

- The investigator is responsible for submitting a continuing review application and to allow sufficient time for the review and IRB re-approval process to be completed before the current approval expires. The IRB approval expiration date is listed on the IRB approval notice and is also within iStar. In order to avoid a lapse in IRB approval, it is recommended that continuing review applications be submitted to the CHLA IRB 60 days before the expiration date.

- Federal regulations make **no provision for any grace period extending the conduct of research beyond the expiration of IRB approva**l. Therefore, continuing review and re-approval of research must **occur on or before the date when IRB approval expires**.

- Continuation of research activities without IRB review and approval is a violation of federal regulations and **represents protocol noncompliance**.

- Investigators are responsible for submitting a continuing protocol in iStar and maintaining current IRB approval until **all** of the following occur:

  - ☐ Subject recruitment has concluded (i.e., no subject recruitment is in progress or anticipated)
  - ☐ All subject specimens, records, data have been collected (i.e., no further collection of data/information from or about living individuals is needed)
  - ☐ All interactions or interventions with subjects are completed (i.e., no further contact with subjects is necessary or anticipated)
  - ☐ Analyses of subject identifiable data, records, specimens are finished (i.e., use or access to subject identifiable data is no longer necessary).

IMPORTANT NOTE:

- Investigators performing industry-sponsored research should discuss study closure with the study sponsor or Clinical Research Organization before formally closing human research studies with the CHLA IRB. Once a study is closed, all data collection and analysis of subject identifiable data and review of source documentation must stop.

Expirations and Lapses in Approval

- Investigators must plan ahead to meet required continuing review requirements. If an investigator fails to submit a continuing protocol application to the IRB or the IRB does not approve the continuation of the research before the date of expiration, **the research must stop**. All of the following research procedures must stop (even if the continuing review application has been submitted to the IRB, all activities must stop until IRB approval is granted):

  - ☐ Subject recruitment or enrollment
  - ☐ Collection of data/information from or about living individuals
  - ☐ All research-related interventions or interactions with currently enrolled subjects*
  - ☐ Data analyses involving subject identifiable data

***Exception**: Research-related interventions or interactions with currently enrolled subjects can continue only if stopping the research would jeopardize the rights or welfare of current subjects. The IRB must make this determination and decide which subjects should continue with the intervention during the lapse.

Investigators who think that currently enrolled subjects are at risk of harm by stopping research procedures, must provide the following information to the IRB:

- ☐ Prepare a written description of subjects who will be harmed.
- ☐ Identify the research procedures that need to continue.
- ☐ Describe the reasons that these procedures need to continue.

An IRB chair will decide whether there is an over-riding safety concern or ethical issue involved such that it is in the best interest of individual subjects to continue to be followed for safety. **However, any information collected during the lapse in approval may not be used for research.**

- Failure to maintain current approval may disqualify data intended for submission to the FDA (e.g., studies of investigational drugs and devices), other federal agencies, and sponsors.

- For studies that are allowed to expire, investigators must include the following information in the continuing review application:

  - ☐ Confirmation that all research activities have stopped.
  - ☐ An explanation of why the study was allowed to expire.
  - ☐ A corrective action plan for preventing lapses in approval and protocol expiration in the future.

IMPORTANT NOTES

- For protocols that are expired for 30 days or more, investigators will be **unable to make any new protocol submissions to the CHLA IRB** until a continuing review application or study closure is submitted for the expired study.

- Protocols that are expired for at least 180 days (6 months) and for which no continuing review application has been submitted, will be closed by the CHLA IRB. **Reactivation of the study will require a new protocol submission for IRB review**. Investigators will be notified of the administrative closure.

- Protocols that are expired for at least 180 days (6 months) and for which a continuing review application was submitted but a response to required conditions of approval have not been addressed, will be closed by the CHLA IRB. **Reactivation of the study will require a new protocol submission for IRB review**. Investigators will be notified of the administrative closure.

Continuing Review Reminder Notices

- The iStar system sends out continuing review reminders at 60, 30 and 15 days before studies expire. A notice of expiration is issued on the date of expiration of each study.

- Investigators are advised to complete the Continuing Review Application within 60 days from the date of the first reminder notice.

Closure Reports

- **A research project no longer involves human subjects** once the investigators have finished obtaining data through interaction or intervention with subjects or obtaining identifiable private information about the subjects, which includes the using, studying, or analyzing identifiable private information. Once all such activities described in the IRB-approved protocol are finished, the research project no longer needs to undergo continuing review.

  - ☐ For example, when the only remaining activity of a research project involves the analysis of **aggregate data sets without individual subject identifiers**, no further continuing review is necessary. At that point the study team can formally close the iStar application.

  - ☐ **Individual subject identifiers include**:
    - ✓ Data about the participants that has **direct identifiers**, and
    - ✓ **Coded data** about the participants that can be re-identified because the study team retains a key code.

  - ☐ **De-identified means no direct identifiers or key codes are linked to the data that could be used to re-identify participants or to collect additional data about participants (e.g., from the medical record).**

- **A study closure or final report is required for all human research studies**. Among other reasons for closing out a study, the closure report updates the IRB on

the conduct and outcomes of the study, any new risks, safety issues or problems that may have arisen since the last study renewal and informs the IRB of the final disposition of research records and data.

- Closure reports should be submitted to the IRB **within 30 days of study close-out** by completing a study closure or final report application in iStar.

- When research activities are complete, simply maintaining individually identifiable private information without using, studying, or analyzing such information is not human subjects research and does not require continuing review.

IMPORTANT NOTES ABOUT CLOSING STUDIES:

- **Do not** file a study closure report if **any of the following six conditions apply**. Such studies must remain active and continue to receive ongoing IRB review and approval:

  - ☐ **Enrollment** at the CHLA-approved site(s) is ongoing.
  - ☐ **Research-related interventions and/or follow-up** at the CHLA-approved site(s) is ongoing.
  - ☐ **Participant follow-up** at the CHLA-approved site(s) is ongoing.
  - ☐ **Identifiable biological specimens** are being maintained or analyzed.
  - ☐ **Data analysis or manuscript preparation** that involves the use or access to personally identifiable information is ongoing.
  - ☐ If there is an external study sponsor and the **sponsor has <u>not</u> provided permission to close the study** with the IRB.

Closing Sponsor-Initiated Clinical Trials

- After study enrollment is closed and interventions with subjects are complete, **do not submit a study closure or final report until the sponsor has closed CHLA as a study site**. This includes:

  - ☐ Sponsor close-out visit is complete, and all outstanding issues have been addressed.
  - ☐ Access to PHI or identifiable data and records (e.g., source documentation) is no longer needed by the CHLA study team, sponsor or sponsor representatives.
  - ☐ All contractual and budgetary issues are complete (e.g., payments to subjects; billing to sponsor or third party insurance).