Tulane University Human Research Protection Program
Guidance on Special Considerations & Reporting Requirements for FDA-, NIH- and DHHS-Regulated Items

A. Investigational Drug Studies

Before beginning participation in an investigation, the Principal Investigator (PI) must commit to the sponsor that he/she will follow Federal regulations governing investigational drugs and devices. The PI must agree to assume the regulations as described below:

1. PI responsibilities: [FDA 21 CFR §312.53(c)(1); 21 CFR §312.60]
   • Conduct the studies in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of participants.
   • Comply with all requirements regarding the obligations of clinical PIs and all other pertinent requirements in this part.
   • Personally conduct or supervise the described investigation(s).
   • Inform any potential participants that the test article(s) (i.e., drugs or devices) are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent and IRB review and approval are met.
   • Report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with §312.64; (f) has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug.
   • Ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
   • Ensure that an investigation is conducted according to the signed statement, the investigational plan, and applicable regulations.
   • Protecting the rights, safety, and welfare of participants under the PI's care.
   • Control of drugs under investigation.

2. Regulations specific to control of the investigational drug: [FDA 21 CFR §312.59; 21 CFR §312.61]
   • The PI will administer the drug only to participants under the PI's personal supervision or under the supervision of a sub-investigator responsible to the PI.
   • The PI will not supply the investigational drug to any person not authorized under this part to receive it.
   • The PI is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by participants.
   • If the investigation is terminated, suspended, discontinued, or completed, the PI must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under

3. Regulations for documentation of investigational drug research studies: [FDA 21 CFR §312.62]
A PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.

Case histories include the case report forms and supporting data (e.g., example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual’s hospital chart(s), and the nurses’ notes). The case history for each individual will document that informed consent was obtained prior to participation in the study.

PI must retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. [21 CFR §312.62]

4. Emergency Use of a Test Article [FDA 21 CFR §56.104(c)]

If all conditions described in 21 CFR 56.102(d) exist (i.e., a life-threatening situation exists in which no standard acceptable treatment is available, and in which there is no sufficient time to obtain IRB approval), then the emergency use exemption from prospective IRB approval may be used for an investigational drug or biological product. [21 CFR 56.104(c)].

Informed consent is required unless the conditions for the emergency use exemption are met. The IRB must be notified within 5 working days when an emergency use exemption is used. Any subsequent use of the test article at the institution is subject to IRB review. This notification must not be construed as an approval for the emergency use by the IRB. The HRPO Director (or designee) will review the report to verify that circumstances of the Emergency Use conformed to FDA regulations. Refer to Tulane’s SOPs for further requirements.

5. Black Box Warnings

A “black box warning” means that medical studies indicate that the drug carries a significant risk or even life-threatening adverse effects. A PI must report to the IRB (i.e., received by the IRB) all unanticipated problem related to any drug involved in research that has a black box warning within 5 working days of the investigator becoming aware of the event.

B. Investigational Medical Device Studies

For medical device studies, each participating PI must sign an agreement with the sponsor that includes a statement of the PI’s commitment to: [FDA 21 CFR §812.43(c)(4)]

- Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA;
- Supervise all testing of the device involving human participants; and
- Ensure that the requirements for obtaining informed consent are met.

1. PI Responsibilities: [FDA 21 CFR §812.100]

- Ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations
• Protecting the rights, safety, and welfare of participants under the PI's care
• The control of devices under investigation

2. PI Must Maintain: [FDA 21 CFR §812.140]

• Accurate, complete, and current records relating to the PI's participation in an investigation:
• All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
• Records of receipt, use or disposition of a device that relate to:
  (1) The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
  (2) The names of all persons who received, used, or disposed of each device.
  (3) Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.
• Records of each participant's case history and exposure to the device. Case histories include the case report forms and supporting data (e.g., signed and dated consent forms and medical records, progress notes of the physician, the individual's hospital chart(s), and the nurses’ notes). Such records will include:
  (1) Documents evidencing informed consent and, for any use of a device by the PI without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual will document that informed consent was obtained prior to participation in the study.
  (2) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each participant upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
  (3) A record of the exposure of each participant to the investigational device, including the date and time of each use, and any other therapy.
  (4) The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
  (5) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

C. Reporting for Humanitarian Use Devices ("HUD")

Extra reporting requirements exist for protocols involving an HUD. When a physician or health care provider receives or otherwise becomes aware of information, from any source, that reasonably suggests that a HUD has or may have caused or contributed to the death or serious injury of a patient, the physician or health care provider has 5 working days to report such findings to the FDA and the IRB as soon as possible. This reporting requirement is in addition to, not a substitute for, FDA and/or manufacturer reporting requirements under 21 CFR 803.30.

D. Human Gene Transfer Research

The PI (lead researcher) of human gene transfer (i.e., gene therapy) protocols have extra reporting requirements when a subject involved in a gene transfer protocol experiences a hospitalization or a death. In addition to reporting them as unanticipated problems to the IRB, they also must reported to the NIH Office of Biotechnology Activities' (“OBA”) as a serious adverse event (using the NIH Serious Adverse Event Report form).
If the gene transfer study is supported by an external sponsor, this reporting also should be coordinated with the sponsor. This must be reported by the PI to the sponsor and IRB within 5 working days. Failure to report gene transfer SAEs to the Federal oversight bodies (FDA, NIH-OBA) may result in sanctions to the Investigator and the Institution.

E. Incarceration of Participants

Incarceration of a participant must be reported by a PI to the IRB (i.e., received) as soon as possible but in all cases within 10 working days of the investigator becoming aware of the event.

Table of Reportable Events & Applicable Time Limits

The following are types of events/problems that require reporting to the IRB. If the event/problem does not fit the category(ies), then the event is not reportable to the IRB. However, the event/problem may be reportable to the sponsor.

<table>
<thead>
<tr>
<th>Event</th>
<th>Deadline to Report to Tulane’s IRB</th>
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<td>Unexpected deaths of a subject involved in either (a) on-site Research (i.e., premises of either the University or TUHC) or (b) off-site Research conducted under the purview of Tulane’s IRB, if such death was possibly, probably or definitely Related to participation in Research.</td>
<td>No later than 48 hours of the Investigator becoming aware of the event. Exception: If an individual dies more than 30 days after she/he has stopped or completed all of the study procedures/interventions and required follow-up, then the PI does not have to report the death promptly when he/she learns of the event. The death may be reported on the Continuing Review Application submitted for the next IRB review. Subjects who do not complete the protocol for whatever reason, including voluntary withdrawal or removal by the PI, are to be included in this reporting requirement if the PI receives information that the former participant has died.</td>
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<td>Unanticipated Problem that is an SAE and that is internal event (i.e., on Tulane or TUHC premises and/or where Tulane’s IRB serves as IRB-of-record for off-site Research)</td>
<td>No later than 5 working days of the Investigator becoming aware of the event.</td>
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<td>Hospitalization or death of subject participating in human gene transfer/gene therapy protocol</td>
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<td>Hospitalization or death caused/contributed by a HUD</td>
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<td>Any event that requires Prompt Reporting to the Sponsor</td>
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<td>Sponsor-Imposed Suspension for risk</td>
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<td><strong>Unanticipated Problem that is an AE and that is <strong>internal</strong> event (i.e., on Tulane or TUHC premises and/or where Tulane's IRB serves as IRB-of-record for off-site Research)</strong></td>
<td>No later than <em>10 working days</em> of the Investigator becoming aware of the event.</td>
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<td>Unanticipated Problem that is <strong>not</strong> an AE</td>
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<td>Breaches in Confidentiality or Privacy</td>
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<td>Any complaint of a participant that indicates an Unanticipated risk or that cannot be resolved by the Research staff</td>
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<td>Incarceration of a participant enrolled in a Protocol not approved to enroll Prisoners</td>
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<td>Addition of a black box warning on any Drug used in your Research</td>
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<td>Change in FDA labeling or withdrawal from marketing of a Drug, Device, or Biologic used in a Research Protocol</td>
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<td>An interim analysis or safety monitoring report that indicates that frequency or magnitude of harms or benefits may be different from those initially presented to the IRB or a paper is published from another study that shows the risks or potential benefits of the Research might be different from those initially presented to the IRB</td>
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<td>Safety monitoring reports and DSMB reports from the Sponsor that do not meet Prompt Reporting guidelines. Safety monitoring reports that indicate a change to the risk to benefit ratio needs to be submitted within 10 days.</td>
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Unanticipated Problem that is an AE occurring at an external site (i.e., not on Tulane or TUHC premises) under the auspices of Tulane’s IRB that, in the opinion of the PI, is both Unexpected and Related or Possibly Related to the Research

No later than *10 working days* of the Investigator becoming aware of the event.

Reports of off-site events occurring in the studies that are completed and closed at the local site should be reported if the event meets the IRB definition as detailed above and the local PI determines that this event may affect risk to participants who have completed the study, which must be reported within *10 working days* of the Investigator becoming aware of the event.
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<tr>
<th><strong>Sponsor IND/IDE Safety Reports</strong></th>
<th>No later than <em>10 working days</em> of the Investigator becoming aware of the event or no later than at Continuing Review.</th>
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<td><strong>Minor Protocol Deviations/Violations</strong></td>
<td>Minor Protocol Violations do not require prompt reporting. They should be reported to the IRB within <em>10 working days</em> of the investigator becoming aware of the violation, or in summary form at the time of next continuing review if not considered a trend.</td>
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<td><strong>Any publication in the literature, safety monitoring report, (including DSM reports), interim result, or other finding that indicates an unexpected change to the risk-benefit ratio of the Research.</strong></td>
<td>No later than 10 working days of the Investigator becoming aware of the event and no later than upon continuing review.</td>
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