From: OC GCP Questions
To: [redacted]
Subject: Consent and DOA Inquiry
Date: Monday, November 16, 2020 1:26:00 PM
Attachments: [redacted]

Good afternoon –

Thank you for your email. I can answer your LAR questions in a general fashion as FDA regulations do not specifically address your questions. The reviewing IRB should have internal written procedures for dealing with specific scenarios. Please see the below information for FDA-regulated studies.

Questions 1/2 - The term "legally authorized representative" (LAR) and is defined in FDA's regulations as "...an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research..." (See 21 CFR 50.3(l)). FDA's regulations provide only limited circumstances in which an investigational product can be given to a subject without first obtaining informed consent from the subject or the subject's legally authorized representative. In general, for studies conducted in the United States, who may serve as an individual's legally authorized representative is determined by State law.

Under 21 CFR 50.3(s) -- Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

Under 21 CFR 50.3(p) -- (p) Parent means a child's biological or adoptive parent.

Please look under 21 CFR 50.3 (l-s) there are other terms that are defined that might be helpful to you.

[Here is a link to all of FDA's human subject protection and good clinical practice regulations: www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm#Preambles .) The terms caregiver is not defined in FDA regulation.

Once a legally authorized representative has been designated for a subject, that individual is responsible for making decisions on behalf of the subject, and to assure that any such decisions are in the subject's best interest..

A legally authorized representative (LAR) is required when the subject is not capable of providing informed consent. Who qualifies as a LAR is determined by local laws and regulations. An impartial witness cannot act as the LAR unless they qualify as a LAR.

You may wish to review FDA guidance documents and websites.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guide-informed-consent

https://www.fda.gov/patients/clinical-trials-what-patients-need-know/informed-consent-clinical-trials

https://www.fda.gov/media/88915/download *(draft)* currently being updated

https://www.fda.gov/media/99271/download

Question 3 - FDA regulations do not specifically address how to make corrections or changes to an IRB-approved document such as the ICF. When the regulations are silent, IRBs, institutions, sponsors, CROs, and investigators are free to develop their own procedures and practices as long as applicable regulatory requirements are met. However, there are some other FDA regulations mentioned below that should be taken into consideration when determining the procedures and practices for making corrections or changes to IRB-approved documents, such as the ICF.

According to the FDA IRB regulations at 21 CFR 56.111(a)(4) and (5) - see www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.111 , and copied below for reference:

Sec. 56.111 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by 50.27.

The IRB typically issues the IRB-approved ICF to be used by the PI/site. IRB-approved documents are usually not altered without a request for a change submitted to the IRB first for consideration.

Also, according to the IRB regulations at 21 CFR 56.108(a)(3) and (4) - see www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.108 , and copied below for reference:

Sec. 56.108 IRB functions and operations.

In order to fulfill the requirements of these regulations, each IRB shall:

(a) Follow written procedures:

(1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;

(2) 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 review;

(3) for ensuring prompt reporting to the IRB of changes in research activity; and

(4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

IRB's are required to follow written procedures for ensuring prompt reporting of changes in the research and likely have a written procedure about the process for making any changes to an IRB-approved document, such as the ICF. It is important to know and follow the IRB requirements. Again, IRB-approved documents are usually not altered without a request for a change submitted to the IRB first for consideration.

Question 4 -The informed consent regulations found in 21 CFR 50.20 say that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject, or the subject's legally authorized representative. Therefore, no study-related procedures may be performed until a subject's consent (or the consent of their legally authorized representative) has been obtained.

Question 5 - There should be no difference in how the study is being conducted at different sites. The study protocol should be followed as written. - Protocol changes/amendments. During the course of a study, a protocol may be formally changed by the sponsor. Such a change is usually prospectively planned and implemented in a systematic fashion through a protocol amendment. Protocol amendments must be reviewed and approved by the IRB, prior to implementation, and submitted to FDA.

Question 6 - A site delegation log is not required in FDA's regulations regarding the conduct of clinical trials (Title 21, Code of Federal Regulations - 21 CFR - Part 312 for drugs and biologics and Part 812 for medical devices). However, it is a recommended document in the ICH E6(R2) guidance document (guidance on good clinical practice – GCP -- https://www.fda.gov/media/93884/download, which is official FDA guidance. (While the ICH document specifies it covers drug and biologics studies only, FDA considers areas related to the general conduct of a clinical trial to be applicable to all studies with FDA-regulated products.) However, this ICH document does not provide details as to who should be included. FDA's guidance document on the supervisory responsibilities of clinical investigators speaks to the need for delegation of study tasks only to qualified personnel (see https://www.fda.gov/media/77765/download). FDA therefore considers it important to document what study task was delegated to whom.

Who should be included on the delegation log - it would be anyone who has an essential role in the conduct of the study. Whether or not the examples you cite, need to be specifically included will depend on the specifics of the study. Those assigned to the study should therefore be listed. If blood

draws are essential to either the timing, dosage, or follow-up of study subjects, the identity of the lab tech, for blood draws, or the medical assistant, for vitals, assigned to the study may also be important to capture. In most cases, this information would not receive major scrutiny if an FDA bioresearch monitoring (BIMO) inspection of the site were to occur.

Since delegation logs are not required by FDA regulations, there is no specific answer to your question as to who has authority over what type of delegation log is used. FDA recommends the sponsor and the sites work together to produce the best method of clinical trial documentation.

Again, because sponsors and sites have the flexibility to adopt procedures that make the most sense to them and their existing business practices,

Kind regards,

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From: [redacted]
Sent: Saturday, November 14, 2020 12:42 AM
To: OC GCP Questions <gcpquestions@fda.hhs.gov>
Subject: Consent and DOA Inquiry

Hello,

I'm seeking guidance on ICF and delegations for observational, minimal risk studies. Specially, the following scenarios:

1. A parent and adult patient, with the mental capacity to provide consent, are both required to complete a consent, as they are both participating in study activities in separate capacities. If the parent inadvertently completed the consent addendum meant for LAR (legal representatives) of patients who do not possess mental capacity to provide consent, but did not complete a consent for their own participation:

a) Is that parent's signature on the LAR of the patient's consent interpreted as consent for their own participation? For clarity, the LAR statement identifies that the signature provided is for enrollment of the patient, not the parent.
b) If not, and the parent is required to provide consent separately, would participation in study activities prior to providing consent *always* be considered a reportable IRB consent deviation?

c) If this person completed study activities prior to providing their own consent (form), could their participation be interpreted as intention of consent?

2. Are there any instances where the consent provided by only 1 parent (of a married couple) to participate in study activities as a caregiver/parent is considered a "blanket" consent for both entities (ie: husband and wife)?

3. Is there such a thing as a consent (execution) error? If so, what are the policies surrounding identification, documentation, and re-consenting?

4. If a trial is approved by IRB A and enrolls a patient; but then changes to IRB B, closing out the study with IRB A; is the patient considered non-consented if there is never an overlap in approval? (Consider scenario: IRB A approved study December 1 2019. Patient enrolls December 15, 2019. Site gains IRB B approval January 16, 2020. Site closes study with IRB A January 20, 2019. Site re-consents patient under IRB B on February 27, 2020.

a. If the patient submits data during the period they are "unconsented", would this be considered participation in a clinical trial without providing consent?

5. Can Good *Clinical* Practices be interpreted differently if studies are not being conducted in a clinic? Specifically, if someone interprets the identification of clinical to be specific to in-clinic trials only, can they override the guidance of these practices with respect to trial execution?

6. In reference to the DOA, what are considered significant trial related duties?

a. If a DOA is not necessarily required, why is it considered such a significant document that is routinely reviewed and requested during monitoring and auditing visits?

Thank you for your time, and I look forward to your insights.

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