From: OC GCP Questions
To: [redacted]
Subject: GCP query
Date: Monday, November 19, 2018 9:59:01 AM
Attachments: [redacted]

Good morning –

This office is not equipped to answer all of your questions. However, we can give you some general references (FDA guidances) for you to review. Additionally, some of your questions relate to institutional policies and procedures and FDA cannot comment on those. We advise you to seek guidance from your institutional officials or the sponsor of your study.

Search for FDA Guidance Documents > Institutional Review Boards Frequently Asked Questions - Information Sheet

Search for FDA Guidance Documents > A Guide to Informed Consent - Information Sheet (LAR and Illiterate Speaking Subjects are addressed in this guidance)

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf (Adverse event reporting)

A discussion related to AE reporting occurs in FDA's guidance "Safety Reporting Requirements for INDs and BA/BE Studies" (available at www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf). This guidance was issued in concert with FDA's final rule, which published on September 29, 2010, "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products." Information on this final rule is available at the following link: www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226358.htm

From an FDA standpoint, we would expect the laboratories used to analyze clinical specimens for clinical trials to be qualified. If the sponsor is using a central laboratory, it would be sufficient for them to retain documentation of the laboratory's qualifications, which usually includes background information on the director. It would, however, seem important to know the reference ranges for the laboratory. Since these can vary from laboratory to laboratory, that information is necessary for the CI to interpret specific laboratory results, particularly when values may be near the upper or lower parts of typical ranges.

In the United States (US) oversight of the conduct of clinical laboratories is under the Centers for Medicare and Medicaid (CMS) as specified by the Clinical Laboratory Improvement Amendments (CLIA). The Clinical Laboratory Improvement Amendments (CLIA), which is under the purview of the Centers for Medicare and Medicaid (CMS) not FDA. Information about CLIA can be found at www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/ and the current CLIA regulations can be accessed at wwwn.cdc.gov/clia/regs/toc.aspx. Therefore, FDA has not issued any regulation or guidance regarding clinical laboratories equivalent to ISO and JCI, as we do not have authority to do so. Most US study sites use a CLIA-certified laboratory for testing required as part of clinical studies. When a study requires a specialized test that is only available at laboratories that may not fall under CLIA (e.g., an academic site), FDA expects to see certification that the laboratory is capable of performing the particular test accurately and reproducibly. For non-US study sites, FDA would expect to see certification/accreditation as required by the country/state in which the study is conducted. If the laboratory in question for some reason lacks such an accreditation, we would need to see evidence that the laboratory is capable of performing the particular testing accurately and reproducibly.

If a site is officially under the company's Investigational New Drug approval (IND) for the study or a non-IND non-US site, FDA would have concerns about accepting data from the site in support of an application or submission if the laboratory used could not be shown to be competent to analyze the samples. For studies that are conducted under an IND, the regulations require the clinical investigator (CI) at the study site to complete and sign a Form FDA 1572. It spells out the obligations of the CI under 21 CFR 312 and, once signed, becomes a contract to abide by the protocol and applicable regulations. The front of that form has a place to enter the name and location of the clinical laboratories that will be analyzing study samples. This is so the sponsor can determine if those laboratories are appropriate for the given study. Therefore, we hold the sponsor primarily responsible for ensuring that the laboratories used are capable of performing the necessary study testing both accurately and reproducibly. However, FDA regulations and international GCP guidelines and laws consider the conduct of a clinical study to be a system of checks and balances, where the sponsor, CI, and independent ethics committee (IEC) have overlapping responsibilities. Therefore, even if the sponsor is remiss in ensuring the quality of the clinical laboratory used, that would not remove the responsibility from the CI/study site to ensure appropriate conduct of the study, which includes analysis of study samples by a laboratory that is capable of producing accurate and reproducible results.

FDA regulations state -

21 CFR 312.56 Review of ongoing investigations.

(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.

(b) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA- 1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of 312.59 and shall notify FDA.
That being said, FDA does not have a guidance document that provides details about how to close out a study. However, the following information is found in the "Guidance for Industry, E6 (R2) Good Clinical Practice: Consolidated Guidance"
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guidance may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

(See section 8.1, stating on page 45 of the ICH guidance)

The activities a sponsor, CRO and investigator/site follow for a close out visit and any data query follow-up are usually addressed in Standard Operating Procedures (SOPs) of the sponsor, CRO, and site. The clinical investigator must ensure that any requirements to maintain IRB oversight per the regulations are met, and additionally, that any pertinent SOPs are followed.

Clinical investigators are responsible for the control of the investigational drug as per 21 CFR 312.61 and to maintain adequate records concerning the disposition of the drug under 21 CFR 312.62(a). The regulations state that if the investigation is terminated or discontinued, the investigator will return or provide the sponsor the disposition of the unused supplies of the drug as per 21 CFR 312.59. In addition to supplying the sponsor with routine progress reports during the investigational study (21 CFR 312.64(a)), the clinical investigator is required to provide the sponsor with adequate information in the form of a final report shortly after the completion of the investigator's participation in the study (21 CFR 312.64(c)).

As per 21 CFR 312.62(c), clinical investigators are required to retain records for a period of two 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 two years after

the investigation is discontinued and FDA is notified. If investigational records are transferred off-site to a third party (e.g., CRO), the sponsor and FDA should be notified by the associated clinical investigator in the form of a final report.

When study enrollment and subject follow-up have been completed at a given site, the clinical investigator will often (usually for FDA-regulated studies) send the required final report to the IRB, thus closing out the study at the site.

FDA's regulations do not specify how to document training for site staff nor do they specify what training is required.

The regulations require that investigators be qualified by training and experience as appropriate experts to investigate the investigational product (see 21 CFR 312.53 and 812.43). The regulations also address documentation of the investigator's qualifications. For drug and biologic studies, 21 CFR 312.53(c)(2) requires that the sponsor obtain the curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation. For device studies, 21 CFR 812.43(c)(1) and (2) require that the sponsor obtain the investigator's curriculum vitae and, where applicable, a statement of the investigator's relevant experience, including the dates, location, extent and type of experience.

Sponsors have discretion in determining what qualifications, training, and experience will be needed, based on the general recognition that this would include familiarity with human subject protection (HSP) regulations (i.e., 21 CFR Parts 50 and 56) and practices as well as good clinical practice (GCP) regulations (see 21 CFR Part 312, for drug and biologic studies, and Part 812 for device studies) and standards (e.g., ICH E6) for the conduct of clinical studies. FDA also expects that any requirements of the jurisdiction where the study is conducted also be met.

FDA holds the clinical investigator responsible for the conduct of the study at his/her site and, therefore, the investigator needs to ensure the qualifications and training of study staff who are delegated study-specific tasks. Such qualifications and training would need to be appropriate for the performance of the delegated tasks. FDA's guidance, "Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects" (available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf) (link above as well) includes a discussion that address qualifications and training of site staff. Following are some excerpts from that guidance:

The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task. Appropriate delegation is primarily an issue for tasks considered to be clinical or medical in nature, such as evaluating study subjects to assess clinical response to an investigational therapy (e.g., global assessment scales, vital signs) or providing medical care to subjects during the course of the study. Most clinical/medical tasks require formal medical training and may also have licensing or certification requirements. Licensing requirements may vary by jurisdiction (e.g., states, countries). Investigators should take such qualifications/licensing requirements into account when considering delegation of specific tasks. In all cases, a qualified physician (or dentist) should be responsible for all trial-related medical (or dental) decisions and care.

The investigator is responsible for conducting studies in accordance with the protocol (see 21 CFR 312.60, Form FDA-1572, 21 CFR 812.43 and 812.100). In some cases a protocol may specify the qualifications of the individuals who are to perform certain protocol-required tasks (e.g., physician, registered nurse), in which case the protocol must be followed even if state law permits individuals with different qualifications to perform the task (see 21 CFR 312.23(a)(6) and 312.40(a)(1)). For example, if the state in which the study site is located permits a nurse practitioner or physician's assistant to perform physical examinations under the supervision of a physician, but the protocol specifies that physical examinations must be done by a physician, a physician must perform such exams.

The investigator should maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., can refer to an individual's CV on file), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.

The investigator should ensure that there is adequate training for all staff participating in the conduct of the study, including any new staff hired after the study has begun to meet unanticipated workload or to replace staff who have left. The investigator should ensure that staff:

*Are familiar with the purpose of the study and the protocol

*Have an adequate understanding of the specific details of the protocol and attributes of the investigational product needed to perform their assigned tasks

*Are aware of regulatory requirements and acceptable standards for the conduct of clinical trials and the protection of human subjects

*Are competent to perform or have been trained to perform the tasks they are delegated

*Are informed of any pertinent changes during the conduct of the trial and receive additional training as appropriate

If the sponsor provides training for investigators in the conduct of the study, the investigator should ensure that staff receive the sponsor's training, or any information (e.g., training materials) from that training that is pertinent to the staff's role in the study.

For investigations conducted under an investigational new drug application (IND), investigators are required to complete and sign a Form FDA 1572. FDA's guidance on this form, "Frequently Asked Questions - Statement of Investigator (Form FDA 1572)" (available at www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf), states, in the response to question 3 in this guidance, "The investigator's signature on this form constitutes the investigator's affirmation that he or she is qualified to conduct the clinical investigation and constitutes the investigator's written commitment to abide by FDA regulations in the conduct of the clinical investigation."

Please see ICH E-6(R2) Guidance section 4 starting on page 13 of the guidance for investigator's Qualifications and Agreements.

Kind regards,

Doreen M. Kezer, MSN
Senior Health Policy Analyst
Office of Good Clinical Practice
Office of the Commissioner, FDA

U.S. FOOD & DRUG ADMINISTRATION

This communication does not constitute a written advisory opinion under 21 CFR 10.85, but rather is an informal communication under 21 CFR 10.85(k) which represents the best judgment of the employee providing it. This information does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: [redacted]
Sent: Saturday, November 17, 2018 8:13 AM
To: OC GCP Questions <gcpquestions@fda.hhs.gov>
Subject: GCP query

Dear Sir,

Very good evening!

Iam writing this mail to have your expert advice on below mentioned questions. It would be really great to have your opinion as per guideline.

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LIST OF QUESTIONS:

Q1) Can a LAR signs informed consent if the subject is illiterate, or else only a impartial witness is required to be present in case of illiterate subject OR a LAR can sign

Scenario 1:

If subject is very old and illiterate and some of the relative (i.e. long distance relationship) has come for ICD process:

Can this long distance relative can sign the ICD in LAR section of ICD. Or

The long distance relative can sign the ICD but the sign need to be in section meant for Impartial witness.

Or other separate impartial witness needs to be present for the ICD process.

Q2) CV and MRC of central lab is available in TMF of a clinical study. However, Is CV and MRC of local lab. Director is required to be filed in TMF of a clinical trial?

Anyways accreditation committees do check CV, MRC and other documents before accrediting any laboratory. So in short if the lab is accredited then they must be having these documents with them.

Q3) Is advance duty delegation by Principal Investigator is acceptable before protocol training of the delegated staff?

Case: In case of contractual staff-If PI is unavailable on study days and is going out due to some preplanned schedule. So can PI delegate some contractual staff in advance for the study and this staff can perform the activity only after conduct of protocol training on that day.

Q4) What is the ideal time for closure of sites which are involved in the conduct of clinical study?

Sites need to be immediately closed after study completion or after CSR finalization and submission to regulatory agency?

Q5) Is it required to sign all pages of Laboratory reports by the PI in order to confirm that PI has reviewed all values or sign. only on last page of the report is sufficient?

Q6) What process need to be followed in case if some Adverse event are still ongoing and Clinical Study Report is finalized and submitted to regulatory agency.

Case: Can we update regulatory agency regarding the AE status when the AE is resolved after initial CSR submission of AE with ongoing status? Or do we have to submit again amended full Clinical study report.

Q7) Case 1: Is more than 2 years of experienced Principal Investigator with MD qualification is required in case of clinical studies related to Phase I study?

Case 2: Less experienced PI with MD qualification can be the PI of phase I study.

Case3: Physician with MBBS qualification with more than 5 yrs. of experience can be the PI of Phase I study?

Q8) Case 1: Is Principal investigator need to be present in pharmacy during dispensing activity or a registered pharmacist can dispense IPs without PI presence for a BABE study?

Case 2: Can a Principal investigator dispense IPs of open label BABE study in absence of pharmacist as PI is trained on all Clinical SOPs.

With thanks,

[redacted]