Manual for Clinical Investigators

Jessica Spivey, BS, CCRC
Executive Director
1-800-785-3150 x 2001
JSpivey@onsiteclinical.com

OnSite Clinical Solutions, LLC

Our Mission
To provide quality research services to individuals who want to conduct a clinical trial.

Our Vision
To achieve premier status as an Investigative Site Network of Physicians by working together effectively as researchers and clinicians to advance scientific knowledge and clinical care.

Our Goals and Principles
Quality, integrity, and accuracy are the goals we strive to achieve. Care is exercised to ensure that each clinical trial undertaken receives the resources and personnel necessary to meet and exceed the expectations of each SMO, CRO, and Sponsor.

Introduction

Welcome to the OnSite Clinical Solutions (OSCS) Investigator Network! By joining our network, you access opportunities to participate in cutting edge research with the support of experienced clinical research professionals to ensure your success as a clinical investigator. Your patients will also gain opportunities to access cutting edge medical therapies and advance medical science as volunteer participants.

It is the determination of OSCS that all of the research supported by its leadership and staff will be of the highest professional and ethical standards. We will make certain that you, as a physician/investigator will have all the educational opportunities, tools and professional support to enable you to carry out your research in full compliance with the ethical standards and regulatory mandates that govern the conduct of clinical trials. We further pledge that each of your patients who volunteer to participate in clinical research will have a safe and positive experience.

The Big Picture

As of 2018, there were nearly 40,000 physicians registered with the FDA as clinical investigators. It is important to note that almost half of all physicians who engage in clinical research try it once but not again. This indicates that many are clearly unprepared and unsupported when they enter the clinical trial world.

OnSite Clinical Solutions is designed to assure that your entry into clinical research will be smooth and successful. We will support you by supplying experienced and trained clinical research professionals to which you can delegate many of the tasks required of clinical investigators with full confidence that your patients will receive skilled and competent care during their participation and that study sponsors will receive clean and valid data in pursuit of FDA approval.

The purpose of this guidebook is to acquaint you with the collaborative processes and support provided by OSCS that will allow you to succeed as a clinical investigator. More specific instruction can be found in the OSCS's Standard Operating Procedures (SOP) manual.

OSCS Operational Model

There are many operational models for conducting clinical research in the medical office setting. In some models, the physician operates his own research center. This includes managing the business considerations, the regulatory burden, marketing, hiring and managing research professionals, IRB and sponsor communications, contract and budget negotiations, patient scheduling, data collection and reporting, adverse event reporting, data query resolution, study drug and device accountability and so on. In this model, the physician/ investigator takes on all the work, accepts all the possible benefits (financial and otherwise), but also all the risks as well. You have chosen OSCS because many or most of the workload

and other considerations are managed and borne by OSCS. This means that OSCS will manage all of the details of the conduct of clinical research except those that cannot be delegated or shared by the Principal Investigator (PI). During the course of the study, OSCS will manage all of the items mentioned above, and reserve only those responsibilities that regulations mandate must rest with the PI. This will leave you in a position to conduct clinical research with minimal impact on your medical practice and yet ensure that your work in clinical research is well compensated. It is important that you understand however, that though OSCS can manage much or most of the operational burden for studies under your purview, regulatory authorities consider you, the PI, as the primary responsible party for the clinical trial and the safety and welfare of the participants. To that end, OSCS will operate in full transparency in this collaboration and make sure that you remain aware and up to date on study progress including the status of all participants and overall study conduct. We guarantee that the personnel assigned to assist you are well trained and accountable and we kindly request that you feel free to communicate with our management and leadership regarding any concerns that arise during the conduct of the study.

Who's Who in the Clinical Research World

Like any other profession, clinical research has its own jargon and set of acronyms. Here is a short list to speed your learning curve. We'll start from the top down:

Sponsor: This is the pharmaceutical company or device manufacturer that is conducting the clinical trials in pursuit of FDA approval. Drug and device studies have some fundamental differences due to differing regulations and processes. OSCS will guide you safety through them.

CRO (Contract Research Organization): This is a company to which the sponsor can delegate all or some of the duties of conducting clinical trials. When a CRO is employed, most or all of the communication takes place with or through the CRO rather than directly with the sponsor.

CRA (Clinical Research Associate): This is the sponsor or CRO's representative that visits the site throughout the study. Initially, this person will conduct site selection activity and monitor the site during the study to audit study conduct and data collection. For this reason they are also called "Monitors".

Medical Monitor: This is the physician employed by the sponsor who manages all medical issues that arise during the trial. On rare occasion, the investigator will speak directly with the Medical Monitor when questions of subject eligibility or adverse events arise.

PI (principal investigator): That's you. The PI is responsible for the supervision of the study at the research site. Many of his duties can be delegated, but s/he remains ultimately responsible for the conduct of the study. For this reason, OSCS will ensure that its team members, to whom you delegate such tasks, are well trained, qualified and skilled.

Sub-I (sub-Investigator): These are medical professionals engaged in the clinical trial to which the PI delegates specific responsibilities or tasks normally assigned to him/her. Since they are also considered investigators, sub-Is are required to have skills and certifications similar to the PI. Qualified sub-I's can include the PI's physician partners (MDs), PA-Cs and Nurse Practitioners. Who qualifies as a sub-I is often dictated by state laws on medical practice. Many of the PI's responsibilities such as physical exams, ECG interpretation, lab reviews, etc. can be delegated to sub-Is. Delegation of tasks is documented on the delegation of authority log.

CRC (Clinical Research Coordinator): This is a research professional who coordinates the conduct of the study at the research site, including subject recruitment, consent, enrollment, study visits, data collection and reporting, data query resolution, adverse event reporting and more. This person, an OSCS professional, will be your primary contact throughout the study.

IRB (Institutional Review Board): This is a federally-mandated committee of at least 5 members of both scientific and non-scientific background that is charged with assuring the rights and safety of research subjects involved in clinical trials. Many institutions (hospitals and universities) have their own IRBs, but there are also independent or "central" IRBs. The makeup and the responsibilities are the same in either case. OSCS will manage all IRB communications throughout the study.

The FDA: The FDA is the regulatory body that oversees the conduct of clinical trials. In addition to enacting the regulations that govern clinical research, the FDA has a Bioresearch Monitoring Program that conducts audits of sponsors, IRBs and research sites (investigators). FDA audits are usually aimed at sites that have the highest enrollment or the most problems (adverse events, protocol violations). In the event of an FDA audit, OSCS will make certain that you are well prepared and supported. FDA audits are discussed in more detail at the end of this manual.

Preparing yourself as a clinical investigator.

Prior to engaging in clinical research it is essential that you understand the ethical guidelines and regulations governing human research. These rules and regulations, contained in the U.S. Code of Federal Regulations and outside the U.S. in the "International Conference on Harmonization E6" document, are collectively referred to as "Good Clinical Practices" or GCP. You will receive education on GCP from OSCS through webinar-based training sessions for new investigators. These will continue quarterly on selected topics that will help you become a skilled and knowledgeable clinical investigator. It is also expected that you will complete CITI training online before you begin participation in clinical trials with OSCS. This course concentrates on the portion of GCP that governs human subjects protections. It will take about 4 hours to complete, which can be accomplished in shorter sessions according to your schedule. OSCS will provide you with the link and an account to begin CITI training. Your certificate of CITI training will become an essential part of the documents that clinical research sponsors will review in qualifying you as a clinical investigator. Additional documents needed

to begin are a current, signed and dated CV and medical license. Please provide your CV in Word format so that it can be modified for OSCS use. We will return it to you for final approval and signature.

There are other resources you can access to increase your knowledge and skill as a clinical investigator. The local chapter of the Association of Clinical Research Professionals (ACRP) holds meetings throughout the year which include educational sessions including CEUs. OSCS will connect you with the local chapter if you would like to participate. Joining ACRP will also provide you a copy of the monthly magazine "Clinical Researcher" which will keep you current with clinical research topics and controversies and connect you with the clinical research community at-large. ACRP also offers certification as a clinical research physician which raises your professional standing with clinical trial sponsors and ensures your placement in upcoming clinical trials. Let us know if you are interested in pursuing this prestigious certification. The remainder of this manual will use the timeline of a typical clinical trial to acquaint you with your role as a clinical investigator and how OSCS will support you through the clinical research process.

Investigator/OSCS Collaboration during the life cycle of a clinical trial

I. Prestudy activity: The first contact from a clinical trial sponsor is in the form of a feasibility or site qualification questionnaire. The purpose of this form is to assess your interest in the study and determine if you have the qualifications, facilities, and patient population to conduct the study. OSCS will complete the form for you, but some items will need your input. The questionnaire will contain a brief description of the patient population (inclusion/exclusion criteria) and type of investigational drug or device to be studied. Any comparator drug or placebo arm will be identified so you will know the kind of treatment your patients will receive in the trial. The questionnaire will include questions about how many eligible subjects you anticipate would be found in your patient database or practice. It is important that this estimate be as accurate as possible. Overestimating the number does not improve your likelihood of being chosen as an investigator since failing to enroll the number anticipated will decrease your chances of future studies with that sponsor. We will work with your staff to perform patient base queries in your EMR to obtain accurate figures if you prefer. This completed questionnaire will be submitted to the sponsor or CRO along with your CV, medical license and training certificates. If the sponsor determines that there is a possible match, the sponsor will send a confidentiality agreement for you to read and sign, after which a full protocol and related materials will be sent for your review. Further information can be found in OSCS SOP #202: "Pre-Study Site Visits". If you want to pursue the study based on your review of the protocol the next step will be:

II. The Site Qualification Visit: This is an on-site visit by a study sponsor or CRO representative to tour the facilities at which the study will be conducted and speak to you regarding your interest in the study. If the study requires special tests, the representative will ask to see the location/equipment used for the test. OSCS will schedule, coordinate, and host this visit. We will work with your staff to arrange the tour and visit any other facilities. Your

presence will be required only briefly, usually at the end of the visit. You will have an opportunity to raise any questions concerning the study, study drug, or study procedures with this representative. If the sponsor finds your site acceptable, OSCS will receive notification of study award. At this point the sponsor or CRO will forward the proposed contract for:

III. Contract and Budget negotiations: OSCS will be the contract holder for the clinical trial, but we will need your input and approval for the final draft. During negotiations, we will work with you to ensure that your portion of the budget will meet your needs and compensate you adequately for your part in the study. OSCS will work with your financial staff to negotiate prices and fees for any tests and procedures performed by you and/or your staff. You will be paid for the procedures you perform and for the time you spend related to the study. In addition to fees for each procedure, you will be paid a "PI fee" for the oversight services you provide related to each study visit. If your participation includes study-related activity in another facility (hospital, surgical clinic, etc), OSCS will negotiate any institutional agreements between the sponsor and facility (Facility Use Agreements) and the prices for items obtained from these facilities to include in the budget. You will be signatory to the final draft of the contract. If you or your practice requires review by your legal counsel, we will coordinate this review and any subsequent edits. The next step is:

IV. The Investigator Meeting (IM): All clinical trials begin with an investigator meeting at which the PI or his qualified delegate (sub-investigator), the study coordinator and/or any other essential personnel are trained in the protocol and study conduct. IMs are typically one to two days in length, usually on the weekend and are in a central location so that all PIs and CRCs can attend. Attendance is mandatory. OSCS will coordinate your attendance, making travel arrangements, etc. The sponsor will pay the expenses related to the event. Reimbursement may or may not be provided by the sponsor, as some consider this "the cost of doing business". When possible, OSCS negotiates payment for your attendance during budget negotiations. This is also an opportunity to network with other physician/investigators and become known by the study sponsors/CROs since sessions are quite often interactive. The real value in the event is that you will have the opportunity to ask questions about the protocol that may present challenges to enrollment or that pose other challenges in execution. At times, features of the protocol may be problematic in execution, and this is the opportunity to point these out to the study sponsor. Very often the protocol is amended after the IM, as PIs point out any weaknesses or problems in study design. More information on IM can be found in OSCS SOP #201; "Investigator and Site Initiation Meetings".

V. Institutional Review Board (IRB) review and approval: As you may know, or will learn in your training, this federally mandated body will be enlisted to oversee the safety and rights of the research subjects participating in each study. OSCS will coordinate IRB review and subsequent reporting and communications. Your part in this process is to review and approve communications and sign some of the regulatory documents prior to submission. Once IRB approval has been granted for the study, we can proceed with the next step, the:

VI. Site initiation visit: This is another on-site visit, usually half a day in length, during

which a sponsor or CRO representative, commonly called a CRA (clinical research associate) or Monitor will prepare the research team to begin enrollment. It includes a review of the protocol, procedures and lab tests, investigational drug receipt and accountability, data collection and reporting and other essential items. Your part in this meeting is to spend about one hour with the CRA to review the protocol and PI role. Prior to this meeting, OSCS will spend some time with you to work out a subject recruitment plan so that the team will know in advance exactly how eligible subjects will be identified and recruited as volunteers. We will share this recruitment plan with the CRA during the initiation visit.

VII. Subject enrollment: This is the most critical part of the clinical trial process. Once potentially eligible subjects are identified in the screening process, they will be invited to participate in the study. This begins with the informed consent discussion. GCP places the responsibility for the informed consent process on you, but you are allowed to share or delegate this to qualified members of the research team under your supervision. Typically, you or one of your participating partners (sub-Investigators) will introduce the study to the patient during the course of usual care, and then refer them to an OSCS team member to continue the consent process. It is important in your interactions with your patients in this setting that they understand the difference between their medical care and their participation as volunteers in a clinical trial. They should be assured that their refusal to participate in the clinical trial will not affect their future medical care. During the consent discussion with the OSCS team member, you, or one of your qualified sub-Investigators must be available to answer questions. You should document your part of the consent process in the patient's medical record. More details on this process are found in OSCS SOP #401.

VIII Study Conduct: Once initial consent is obtained and documented, the OSCS Clinical Research Coordinator (CRC) will perform a thorough screening of the medical record to assure eligibility and execute any screening tests and questionnaires including the collection of a thorough medical history. Your part in the screening visit usually includes a complete physical exam and/or other exams that require a qualified and licensed MD or PA. Before a subject is randomized, you or a qualified sub-Investigator must make the determination that the subject is eligible, based on comparing screening results with the inclusion/exclusion criteria described in the clinical protocol. Once enrolled and randomized, the CRC will schedule and coordinate all the subject's visits throughout the study according to the investigational plan. S/he will work with your clinic staff for scheduling. You will be notified when and if any of the visits require your direct involvement and what you are required to do at these visits. A file with "source documents" will be created and maintained by the CRC. This source record contains all of the data that will be reported to the study sponsor. You will also record your study activity in this record and also note in the subject's clinic chart any relevant information. More information on this process is found in OSCS SOP #403 "Subject Management While On Study".

During the conduct of the study, lab results will be received and adverse event reports collected from the subject. It will be your responsibility to review lab results and determine the clinical significance of any abnormal findings. You will also determine whether any reported adverse events may be related to the study drug. Serious adverse events must be reported to the IRB

and sponsor within 24 hours of discovery. OSCS will coordinate this reporting process, but you must contact OSCS immediately when you learn of any serious adverse events so that the reporting may begin. More details on this process are found in OSCS SOP #405; "AE Reporting".

During the progress of the study, the sponsor or CRO will send a CRA to audit the study records about every month or six weeks. The CRA will usually perform source data verification on all activity since the previous visit. This requires access to both the study records. The CRC will work with your staff to schedule this visit. The CRA will meet with you and the CRC briefly at the conclusion of the visit to share his/her findings. It is essential that you are available for this short visit as it demonstrates your oversight and involvement in the study. The CRA represents the eyes of the sponsor, so your participation in these visits is critical to your relationship with the sponsor and any future study opportunities with them. Further details are found in OSCS SOP #304; "Sponsor/CRO Visit".

During the enrollment period, OSCS will coordinate IRB communications and study renewals, which typically occur on a yearly basis. These reports will be circulated to you for review and approval prior to submission.

OSCS management will work with you during the enrollment period to review recruitment levels and the effectiveness of the recruitment plan. You will also have the opportunity to report any concerns you have with the progress and conduct of the study. Payments will be reported to you and forwarded according to the study contract and budget.

IX. Study Closeout: At the conclusion of the study, the CRA will visit the site to close out the study. This requires the resolution of any outstanding data queries, which will be managed by OSCS. At this visit, OSCS will coordinate final disposition of any remaining study drug. OSCS will also submit a closeout report to the IRB and manage the retention of study records according to regulatory requirements and sponsor preferences.

X. Other Study Events:

FDA audit: The FDA conducts a Bioresearch Monitoring Program to maintain compliance with the regulations governing human research. Most research sites that have been in operation for more than 5 years have had at least one FDA audit. During the audit, the FDA inspector will interview the investigator and CRC and examine all study documents. The inspector's aim it to ensure that the data in support of the sponsor's application to approve the drug is valid and accurate and that the rights and safety of the subjects enrolled in the study were protected. It is expected that the investigator will be available during the inspection, which typically lasts less than one week. Findings in the wake of an FDA audit are classified as NAI (No Action Indicated) which means that the investigator followed all the regulations governing clinical research, VAI (Voluntary Action Indicated), which means that there were lapses in compliance with regulations and OAI (Official Action Indicated) which means that

serious violations of regulation were present and the investigator is subject to official action by the FDA. About 46% of Clinical Investigator audits result in VAI findings which are summarized in an FDA form 483. The investigator is required to respond to a 483 within 14 days. Inadequate response to a 483 can result in an FDA Warning letter, which can further escalate to official action. OAI findings are very rare and typically involve fraud or falsification of data. OSCS will coordinate and provide support in preparation for and during the conduct of an FDA inspection. In the event of a 483, OSCS will assist the investigator to create a thorough and well-prepared response. Most investigators find that an FDA audit is a good learning and quality improvement opportunity. They are often glad to have one "under their belt" as it can serve to validate their skill as a clinical investigator. OSCS's ongoing training for clinical investigators includes preparation and conduct during FDA inspections.

Sponsor Audits: When a sponsor submits a final application for a new drug approval to the FDA, the FDA usually audits the top enrolling sites in the clinical trial. For this reason, the Sponsor will audit top-enrolling sites in anticipation of an FDA audit to follow. The goal is to ensure that the site is well-prepared for the FDA inspection. If an FDA audit does follow the sponsor audit, a sponsor representative will be on-site to assist the site for the duration of the FDA inspection.