



Best Practices for US-Based Sponsor-Investigators and their Institutions

THIS DOCUMENT SHOULD NOT BE CONSTRUED AS PROVIDING LEGAL ADVICE. EACH ORGANIZATION HAS ITS OWN UNIQUE PROGRAM GOALS AND LEVEL OF RISK TOLERANCE. ULTIMATELY, EACH ORGANIZATION SHOULD CONSULT THEIR MANAGEMENT STAFF AND LEGAL COUNSEL WHEN DESIGNING THEIR IISR PROGRAM.

THE OPINIONS EXPRESSED BY THESE AUTHORS DO NOT NECESSARILY REFLECT THE THOUGHTS/OPINIONS OF THEIR EMPLOYERS.

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INTRODUCTION 3

PRINCIPAL INVESTIGATOR CONSIDERATIONS..... 4

IDENTIFYING PARTNERS AND SUPPORTERS..... 5

PROTOCOL AND CONSENT DEVELOPMENT..... 7

IRB CONSIDERATIONS..... 8

CLINICAL INVESTIGATIONS EXEMPT FROM FILING 8

REGULATORY RESPONSIBILITIES 9

REQUIRED CLINICAL STUDY RESOURCES..... 13

RECRUITING AND SCREENING CAPABILITIES..... 18

FACILITY CONSIDERATIONS..... 23

MULTI-SITE RESPONSIBILITY 25

CONCLUSION..... 26

APPENDIX 1: REFERENCES..... 27

APPENDIX 2: DEFINITIONS AND ABBREVIATIONS 30

APPENDIX 3: STAFF AND SITE CHECKLISTS..... 38

APPENDIX 4: BUDGET CHECKLIST 42



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Introduction

The purpose of this document is to provide guidance and assist sponsor-investigators and study staff in navigating the complex environment that is Investigator Initiated Sponsored Research (IISR). While there is an emphasis on US laws and the requirement to submit investigational new drug applications (INDs) or Investigational Device Exemptions (IDEs), it should be noted that this document is intended to be an overview of the concepts and is not meant to include all requirements that apply to IND and IDE submissions.

Regulations are written for sponsors and investigators, and as a sponsor-investigator you assume the roles and responsibilities of both sponsor and investigator. Hence, throughout this document the terms sponsor and investigator may be used interchangeably due to the shared obligation assumed by the sponsor-investigator.

What is the definition of Investigator?

The individual who actually conducts the investigation [\[21 CFR 312.3\(b\) and 812.3\(i\)\]](#).

Who is a Sponsor?

The FDA defines a sponsor as one who takes responsibility for and initiates a clinical investigation [\[21 CFR 312.3\(b\) and 812.3\(n\)\]](#). The sponsor does not actually conduct the investigation, unless the sponsor is a sponsor-investigator. A sponsor can be an individual, pharmaceutical company, governmental agency, academic institution, private organization, or other organization.

What are the Types of Sponsors?

There are 2 types of sponsors: Regulatory [21 CFR 812.3\(n\); 312.3\(b\)](#) and Financial [21 CFR 54.2\(h\)](#). A regulatory sponsor is responsible for holding the IDE/IND, and for fully complying with the regulations regarding the submission. In an investigator-initiated study, the investigator also serves as the regulatory sponsor. The financial sponsor provides funding and/or product to complete the study.

What is meant by a Sponsor-Investigator?

A Sponsor-Investigator is an individual who both initiates and conducts an investigation [\[21 CFR 312.3\(b\) and 812.3\(o\)\]](#). As defined by the FDA, the sponsor-investigator term refers only to an individual and no other entity. Under this definition, this individual must then comply with both the requirements of an investigator and a sponsor. These primary requirements broadly include the submission and maintenance of the IDE and/or IND.



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If an individual assumes the role of a sponsor-investigator, they then assume the responsibilities of both the sponsor and the investigator. An example of this, is that in the case of multi-center trials, the sponsor-investigator is responsible not only for ensuring regulatory compliance at their own site, but also at any other sites listed under their IDE and/or IND.

Principal Investigator Considerations

The FDA has separate regulations for the principal investigator of drug or device clinical trials, however the considerations for both are fundamentally the same, and this section seeks to address the overarching responsibilities for both. The specific responsibilities for drug studies are provided in [21 CFR 312](#) as well as [Form FDA 1572 \(Statement of Investigator\)](#), while the obligations for medical studies are laid out in [21 CFR Part 812](#). In medical device studies, there must be a signed agreement between the investigator and sponsor in lieu of the Statement of Investigator.

Those planning to conduct IISRs should consider what experience and knowledge are necessary prior to conducting the study, regulatory responsibilities, supervising obligations, staff training, resource allocation, study subjects, recruitment and screening, and the available time to devote to an IND/IDE study.

Experience and Knowledge

In order to responsibly conduct an IND/IDE trial as a principal investigator, the investigator should have acquired prior experience leading and assisting in clinical studies. This is critical so that the investigator understand the different phases of clinical studies ([ucm405622](#)) and the various clinical trial designs ([ucm201790](#)). Additionally, the principal investigator needs to be familiar with all relevant FDA regulations in Title 21 of the Code of Federal Regulations (CFR), and guidance documents ([ucm446695](#)) as they are solely responsible for compliance with all governmental regulations. Likewise, they must be prepared and able to navigate the ambiguities of FDA responses after the receipt of the IND/IDE in order to assess whether they have permission to move forward with the study ([ucm446695](#)). Related to the nuances of the FDA responses, the investigator must understand what constitutes “valid scientific evidence,” and be able to assess whether their study meets that definition ([21 CFR 860.7](#)). Also, situations will arise when the investigator will have to amend the study and submit it to the FDA, and must understand the requirements that go along with amendments ([ucm446695](#)). If one is unsure of whether an amendment needs to be filed, a consultation with CDER/CBER can be setup to gain clarification. In order to successfully file a document submission to the FDA,



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the principal investigator should possess a level of proficiency in portable document formatting (pdf) and electronic storage options ([ucm446695](#)) ([21 CFR 312.22](#)).

Furthermore, it is expected that investigators have a record of producing quality research, which has been published in credible peer reviewed journals. If possible, past published research should be as similar to the proposed study to ensure their past experience is translatable to the prospective study in terms of scope and requirements. Young investigators greatly benefit from first working under a senior investigator on their research projects, and then having the senior member continue to work beside them on their first study as the Sponsor-Investigator.

Investigator Considerations for Device or Drug Studies

In addition to past experience, the investigator needs to be competent in delineating whether their study involves a drug, biologic, medical device, or combination ([21 CFR 312.23](#)) as each carries different regulatory implications and burdens. It is also necessary for the investigator to understand when a nutritional supplement or cosmetic is a drug for the purpose of the research study ([ucm229175](#)).

For instance, if the investigator is studying a medical device, they need to be aware of what constitutes consideration for Humanitarian Use Device (HUD) or Humanitarian Device Exemption (HDE), and how the application processes differ ([21 CFR 814.102](#)). If they intend to pursue HDE status for a device, the intent needs to be documented in the IDE application ([ucm389154](#)). Some investigators may be surprised to realize that studies which utilize an unapproved diagnostic test, may fall under the regulations for medical devices.

If the study involves a drug, the investigator is responsible for being knowledgeable about the investigational drug's pharmacokinetic, toxicological, chemical, safety profile, CMC, and previous clinical trials ([ucm446695](#)). Furthermore, it is required that they be familiar with and knowledgeable regarding labeling requirements for the drug to comply with regulations. Trials that include the investigational use of psychotropic substances require disclosure of its abuse potential, and radioactive substances require that clear dosing calculations are taken to track total absorption for each subject ([ucm446695](#)).

Identifying Partners and Supporters

Experienced sponsor-investigators should already have a general idea of the existing drugs and/or devices relevant to his or her particular area of expertise through popular journal



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subscriptions, attendance at medical congresses, and participation in relevant industry-related technical working groups with partners and donors. Pay close attention to organizations who fund plenary or educational sessions and take time to visit their booth, if there is one. Most of the time you can get a general sense of the overall mission of the organization and whether they have the resources to support research proposals through these events.

Searching [PubMed](#) and [clinicaltrials.gov](#) are two other easy ways to determine if there are organizations supporting research within your field and finding other investigators with similar research interests. Look for research that may be similar to your idea and highlight the aspects of your research that make it unique. Whenever possible, try to avoid proposing research that competes with other ongoing studies at your own institution in an effort to ensure that research completes on schedule.

Drug and Device Manufacturers

Most drug or device manufacturers that support IISRs will have instructions on their website on how to apply and what types of support are covered. Unfortunately, there is no consistent placement or terminology for this type of research; some common acronyms are IIR, IIS, ISS, IST, IIT, and ESR. Websites usually include information about this type of research under the sections for R&D or HCPs, and many companies will publicly or semi-publicly post their high-level areas of interest for each product. Keep in mind that a company's interest in supporting IISRs is typically greatest between the FDA approval of a product and 2 years prior to the product going generic. Major exceptions to this are device and oncology drug products, which typically support IISRs earlier to support registration filings or to provide proof of concept in a new disease indication.

Prior to submitting your research proposal to the company, it may be helpful to speak with one of the company's Medical or Clinical Science Liaisons. They will be able to answer most questions that you may have about the clinical experience of a product and can provide a high-level overview of the review process, including timelines. Each company operates their review cycle differently and there can be rolling, batch or annual reviews at local, regional, and/or global levels of the organization, and knowing the review timelines will allow you to better plan for other research activities.

Other Supporters

In addition to drug and device manufacturers, there are a multitude of other granting institutions. In the United States, the federal government supports numerous research endeavors and requests for grant applications are [posted publicly](#). In healthcare, many of these are through [CDC](#), [DoD](#), [HHS](#) or [NIH](#) grants.



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There are also many non-profit institutions that provide independent grants. Some are primarily government funded, as is the case of the [NCI's cooperative groups](#), and some are primarily private funded, as in the case of many patient advocacy organizations. A quick internet search of the disease area and "foundation" or "grant" usually will provide a few different options, however, applications are usually most successful when you discuss them with a liaison within the foundation prior to submission. Dedicated physician networks can be very helpful in obtaining support, but keep in mind that the more parties are involved, typically the slower the research is to get started.

Protocol and Consent Development

The study protocol outlines the research activities in full and development and maintenance of this document is the responsibility of the investigator-sponsor. On March 17, 2016, NIH and FDA jointly [released a Draft Clinical Trial Template for public comment](#).

Many individuals may need to contribute to the study protocol, so it is necessary to have a process for making updates to drafts in order to maintain sufficient document control. At minimum, the protocol should include enough background information to understand the study hypothesis, criteria for subject inclusion or exclusion, a complete list of study procedures, a description of the investigational drug or device, and the statistical plan, including the sample size and power calculations.

The informed consent form (ICF) contains similar, but abbreviated, content as the protocol. The ICF also includes a complete description of all known risks and potential benefits of the study interventions. The ICF must also contain the 8 required and 6 additional elements as described in the regulations for protection of human subjects ([21 CFR 50.25](#)). Its purpose is to adequately describe the protocol in terms that a layperson could understand, so that the subject can make an informed decision on whether they would like to participate in the research.

If a drug or device manufacturer is providing support for the research, they will typically request to see a copy of the protocol and ICF prior to these documents being submitted to the IRB. When working with multiple organizations, it is important to incorporate the review timelines of each of the reviewing parties into the overall study plans in order to have accurate timelines.



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IRB Considerations

To ensure that the rights, safety, and welfare of subjects are properly maintained all studies should be properly vetted and reviewed by Institutional Review Board (IRB). It is the duty of the IRB to assess the adequacy of all research sites to be involved in the study, and determine whether the proposed sites can satisfy criteria set forth by the FDA ([ucm366335](#)) ([21 CFR 56.107](#)). Due to the importance of the IRBs both in terms of ethical considerations and protocol finalization, the investigator must have a moderate level of IRB experience to advance their protocols.

When reviewing a study, IRBs should ask the clinical investigator whether an IDE/IND is required, and if not then what is the basis of that determination. The IRB may make their approval conditional on the sponsor submitting an IDE/IND is required ([ucm366335](#)) and any decision on the part of the IRB to approve, disapprove, or modify the trial's research activity must be done in writing. If the IRB disapproves of a study, it is in best practice for the IRB to provide adequate rationale for the decision to allow the investigator to rectify the areas of concern. In general the IRB should be cognizant of the sensitivity and confidentiality of information discussed at the meetings, and should be implementing measures that protect any confidentiality ([ucm126425](#)).

As previously eluded to the principal investigator is responsible for understanding how the IRB functions, and in turn accountable in ensuring the rights, safety, and welfare of any human study subject and staff of the study are protected. Furthermore, it is the obligation of the principal investigator to make certain the IRB being used is in compliance with FDA regulations ([21 CFR 312.60](#), [21 CFR 56](#) and [60](#)).

Clinical Investigations Exempt from Filing

Prior to contemplating submission of an IND, the investigator has to determine whether the study actually requires an IND based upon the criteria set forth by the FDA ([ucm366335](#)) ([ucm229175](#)) ([21 CFR 312.2](#)). When in doubt, the sponsor should either contact the FDA for clarifications for submitting an IND/IDE rather than proceeding without one. If the FDA feels that the research meets the criteria for exemption, they will provide a written response to that effect which should be stored in the trial master file.



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IND Exemption Criteria

FDA regulations describe two categories of clinical investigations that are exempt from the IND requirements described in part **21 CFR 312 (ucm229175)**. Broadly speaking the two categories of investigations, which are exempt are those that include those using marketed drug products (other than for medical practice), and studies in humans aimed at bioavailability and bioequivalence data using unapproved versions of approved drug products (**21 CFR 320.31**). There are numerous criteria that must be met under each category of exempt clinical investigations (**21 CFR 312.2(b) and 320.31(b)**). In addition to these two categories of exemptions, the FDA has provided guidance on INDs for drugs and biological products aimed at treating cancer. Regulations in **21 CFR 312.2(b)(1)** provide for the exemption of products to treat cancer if they meet required criteria, which investigators involved in oncology research should be familiar with (**ucm071717**).

IDE Exemption Criteria

The investigational device exemption (IDE) regulation **21 CFR 812** describes the three types of device studies: significant risk (SR), non-significant risk (NSR), and exempt studies (**ucm126418**). Sponsors should be familiar with the categorization of medical devices and be comfortable interpreting guidance provided by the FDA. Typically, studies involving an already cleared medical device in accordance with the indication on the label are exempt from **Part 21 CFR 812**. The risk determination is based on the proposed use of a device in an investigation, and not on the device alone. IRBs should consider the potential harm the procedure could cause as well as the potential harm caused by the device.

If the medical device is going to be studied under a new use, then the investigation must comply with IDE regulations. Similarly, studies conducted on PMA approved devices are exempt from IDE requirements as long as the study is in line with the approved labeling (**ucm127067**). It should be noted that if a device is exempt the investigator is still responsible for complying with **21 CFR Part 50** and should comply with **21 CFR Part 56. 21 CFR 50.1(a), 21 CFR 50.20, 21 CFR 56.101(a), and 21 CFR 56.103**.

Regulatory Responsibilities

Sponsor-investigators must understand that they are ultimately accountable for planning, maintaining, and submitting the IND, regardless of whether they delegate those responsibilities to another member of their research staff (**ucm446695**). Upon receipt of the IND, the FDA will send an IND acknowledgment Letter, which will include the IND number, division contact, and official FDA date of receipt. A proposed trial cannot be initiated until 30 days after the FDA's



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confirmed date of receipt ([21 CFR 312.23](#)) or until the FDA issues a notice that it is safe to proceed. The sponsor-investigator should always supply the agency with accurate contact information so that communication with the FDA is both direct and timely.

Sponsor-Investigator Oversight of Studies

The FDA may place a proposed or ongoing trial on clinical hold at any time as outlined in [21 CFR 312.42](#) and investigators should familiarize themselves with criteria the FDA uses in determination of assessing whether a study regarding an IND gets put on clinical hold. The FDA can issue both partial (specific restrictions) or complete holds (study must completely halt or not begin). Within 30 days of the sponsor-investigator being notified of the hold, the FDA will send a written letter detailing why the study was put on hold, and what the investigator must do to remove the hold. In some instances, the FDA will completely shut down a study rather than putting a study on hold, and criteria for shutting down a study should be understood ([ucm446695](#)).

Not only is an investigator responsible for understanding the proper protocol for clinical trials, they are accountable for being familiar with FDA inspections of clinical study sites. Typically, the FDA will try and implement remedial steps with the study investigator before placing a hold on the trial. A signed [Form FDA 1571 \(Investigational New Drug Application\)](#) affirms that investigators agree to refrain from beginning, or continuing a clinical trial covered by an IND, if the trial is placed on hold.

If a study is withdrawn or inactivated for safety reasons, the FDA requires a written report of the reasons, and if a device or drug manufacturer is providing financial support they will generally require a copy of the documentation that is sent to the FDA. There are specific steps that need to be taken when investigators themselves decide to withdraw, inactivate, or reactivate a IND in order to stay in compliance with FDA regulations ([ucm446695](#)) ([21 CFR 312.38, 44, 45](#)).

FDA regulations provide for three major categories of decisions: approval, approval with conditions, and disapproval. In order to understand whether the FDA has the authority to disapprove of the IDE application, investigators should understand the Food and Drug Administration Safety and Innovation Act of 2012 in addition to [21 CFR 812.30](#). Approval with conditions tends to be reserved for situations when there are outstanding issues that do not raise concerns that would preclude the initiation of the clinical investigation, however, it needs to be understood that these concerns will be addressed.



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IND Submission Components

As part of the submission of the IND, to the FDA there needs to be an investigator's brochure (when applicable), clinical trial protocol, CMC, pharmacology and toxicology information, and summary of previous human clinical trials. If the drug manufacturer is providing support for the research, they will generally want to either view and/or approve the final version of the protocol prior to the IND submission to the FDA. An environmental assessment must also be conducted to understand the impact the study product may have on the environment ([ucm446695](#)) ([21 CFR 312.23](#), [25.31](#)).

If an investigational new drug under an IND is imported, the sponsor-investigator becomes responsible for complying with the requirements found in [21 CFR 312.110 \(a\)](#). It is important to be aware of these rules even when dealing with a drug or device manufacturer based in the United States; while most companies have finishing facilities within the United States, there may be instances where product will need to be imported from other facilities. Export of a study drug falls under [21 CFR 312.110 \(b\)](#).

Chemistry, Manufacturing, and Control (CMC) information for the drug under study should be included in the IND as outlined in [21 CFR 312.23\(a\)\(7\)](#). The scope of the CMC information depends on whether the drug in question has already been lawfully marketed in the US or has been previously filed under an IND. If the drug is lawfully marketed, the New Drug Application (NDA) holder should submit a letter to FDA authorizing cross-reference to their IND in support of the sponsor-investigator's IND. A copy of this letter must be included in the sponsor-investigator's IND.

- a. If the drug has a previous IND, the previous labeling from those applications should be used with a statement stating the dosing and administration will follow that previous labeling.
- b. If the drug is not legally marketed in the U.S. and has no existing IND, then complete CMC information must be provided.
- c. If the drug is not legally marketed in the U.S. but does have an existing IND, then a letter of cross reference authorization must be provided by the supporting drug manufacturer.
- d. If information from the original manufacturer is not available, the FDA may consider drug history and clinical setting to determine alternative CMC prerequisites.



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Studies that take place in a foreign nation requires that the investigator not only understand the FDA regulations, but that they familiarize themselves with the rules and regulations governing clinical trials in each particular nation to ensure they are in compliance ([21 CFR 312](#)). The [International subpage](#) of the US Department of Health and Human Services is a good place to start looking for information, as is the European Parliament of the Council ([2001/20/EC & 2005/28/EC](#)) and the [Ministry of Health Labor and Welfare](#) in Japan, however your best resource will be the regulatory personnel that support the activities of participating sub-investigators.

Monitoring Considerations

FDA regulations require that a clinical study monitor be appointed by the sponsor to oversee the progress of the investigation ([21 CFR 312.53; 812.43 and 812.46](#)). As a sponsor-investigator the investigator is allowed to assume this role, however, there must be thorough documentation of the monitoring plan as well as all monitoring activities. It is expected that the sponsor provides the FDA with a detailed monitoring plan, which includes a brief description of the study, its objectives, critical data, study procedures, and required staff training. The plan is supposed to communicate specific risks to be addressed by monitoring. A qualified internal candidate or contract monitor may be appointed, and they should be screened for appropriate and translatable clinical knowledge to the prospective study at hand as well as all regulatory responsibilities that are assumed by the role.

In recent years, the FDA has released guidance and recommendations for risk-based monitoring due to the complexity of clinical trials often times spanning multiple sites ([ucm269919](#)). For example, the sponsor should incorporate centralized monitoring practices, rather than relying on on-site monitoring. Additionally, a statistical approach may provide the best protection against data anomalies, which could serve to alert the sponsor that a site visit may be imperative. Centralized monitoring can be utilized to monitor sites that may be prone to more risk based upon their characteristics (i.e. withdrawal rates, eligibility violations, delays in reporting data, and non-compliance). Monitoring activities should revolve around preventing and mitigating important and likely sources of error. Due to the sheer responsibility involved in monitoring the clinical trial, it can be a prudent decision to look externally for an experienced study monitor. Regardless of who the study monitor is for the trial, any monitoring activities must be properly documented according to regulations ([ucm269919](#)). Essentially, the documentation needs to provide enough detail to allow verification that the monitoring plan was followed per protocol.

For Phase I trials, an outline of the clinical trial that details the subjects, dosing plan, and safety considerations is all that is required. For Phase II and III trials, complete detailed protocols must be submitted to encompass all aspects of the purpose, sponsor investigator info,



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selection/exclusion criteria, trial design, dosing plan, measurements, monitoring and testing procedures. These protocols must show IRB approval ([ucm446695](#)). Phase I, II, and III information only relate to drug studies, as medical device clinical trials fall into different classifications.

Required Annual Filings

Within 60 days of the anniversary date that an IND went into effect, a sponsor-investigator is required to submit a brief annual report regarding the progress of the trial ([ucm446695](#)) ([21 CFR 312.33](#)). The report must contain information regarding adverse events, subject dropouts and corresponding reason for dropout, any new information related to the product's action (i.e. dose response), individual trial progress with results, and the investigational plan for the coming year. In addition to submission of documents to the FDA, the sponsor-investigator is required to submit reports annually to the reviewing IRB ([21 CFR 56.109\(f\)](#)), and normally supporting drug manufacturers will require copies of correspondence with the FDA to be provided as a copy to them as well.

Under [21 CFR 812.150\(b\)\(5\)](#) sponsors-investigators are required to submit at least annually progress reports to the reviewing IRB. If the IDE is for a medical device that has been classified as a significant risk device, the sponsor must submit progress reports to the FDA. It should be noted that investigators who have not assumed the dual role of sponsor-investigator may have had experience with annual reports, however, the former differed in that there were no regulations stipulating the format or content of the annual progress reports. Specific requirements and format of the sponsor IDE progress reports can be found on the FDA website in section [812.150](#).

Registering the Trial on ClinicalTrials.gov

Once the IND or IDE has been approved, [Form 3674](#) must be completed to register the IND or IDE trial, and all relevant results submitted to the clinicaltrials.gov website database ([ucm446695](#)). Information on how to register your study can be found [here](#). Per the Food and Drug Administration Amendment Act (FDAAA) of 2007, sponsors are required to register their trials on ClinicalTrials.gov, and this must be done according to defined deadlines. Registration on ClinicalTrials.gov is also a requirement for publication in many medical journals per the [International Committee of Medical Journal Editors \(ICJME\)](#).

Required Clinical Study Resources

Sponsor-Investigator Time Commitment



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If time is truly a scarce resource, an investigator needs to think twice about initiating a IISR. Due to the sheer number of responsibilities and obligations shouldered by the sponsor-investigator, there is a considerable time commitment involved with IISRs above and beyond research sponsored by the drug or device manufacturer. Aside from day-to-day operations of the study, regulatory filings and submissions require long-term planning of the staff and financial resources necessary at each of the various phases of the study. Progress of the study should be tracked against the original timelines and significant delays or resource constraints should be brought to the attention of all relevant staff so that appropriate contingency plans can be made. Often times strict deadlines for submission and meetings with the FDA are necessitated to prevent significant delays in progress of the studies, and to make certain these are met the investigator needs to have the ability to block off time from all other responsibilities around vital dates. Awareness among study staff regarding critical deadlines and deliverables should be widespread to keep the study on time.

Supervision of the Study and Staff

As defined by the FDA, the investigator of the trial is the one who actually conducts the trial, and under whose immediate direction the investigational drug is administered or dispensed to the subject ([ucm446695](#)). Dispensing and administration of the product is only a small portion of scope of supervisory duties, for instance the investigator must maintain compliance among all study staff in accordance with the scope of regulations.

While it is common practice to delegate tasks to assistants, and perhaps third party affiliates, the principal investigator is ultimately responsible for providing a sufficient level of supervision and training to those completing delegated tasks. The FDA will hold the sponsor-investigator responsible for any regulatory violations they deem a result of inadequate supervision of the study. When assigning responsibilities to study staff members, it is the duty of the investigator to determine their depth and breadth of involvement based upon their level of training ([21 CFR 312.3](#)). Study staff should be made aware of the roles and responsibilities of all members of the team. Changes to the staff, or their duties need to be updated on a regulatory checklist to ensure compliance.

It is the responsibility of the investigator to track any special certifications that are required for themselves as well as any study staff. If training or certification is expected to expire during the course of the study, they must be renewed to be in compliance with regulations. The documentation for all training and licenses should be maintained in a fashion that enables them to be easily accessed during an inspection.

Moreover, the investigator is obliged by regulations to ensure that their study staff have no documented FDA or IRB violations, and if violations are present the investigator must



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determine whether the study staff is eligible to participate. The FDA maintains several [lists on its website](#) of individuals who have been debarred or restricted, are in the midst of disqualification proceedings, or have received warning letters based on FDA inspections. These lists include individuals as well as organizations, and sponsors should ensure that appropriate safeguards are in place if they make a decision to work with any individuals or organizations included in these lists.

Staffing

Physicians and medical staff are generally not sufficient to meet all the various demands of a clinical research study; it is important to have staff members that are focused on the more operational or logistic needs of a study. Larger academic institutions usually have staff dedicated to regulatory filings, negotiating study contracts, assuring appropriate intellectual property ownership, or developing and maintaining study budgets. While smaller institutions may not have the luxury of having specialized staff, it is still a good idea to have someone available to support the sponsor-investigator in evaluating these aspects, which may not be directly within the investigator's area of expertise.

The investigator, in collaboration with logistics staff members, should thoroughly inspect the protocol of the study to identify the resource requirements of each step. Individual staff members should be assigned to the task of constant inspection of supplies, and monitor usage as well as study alterations. Alterations to supplies and a running inventory should be recorded in the master document. It is also important for the sponsor-investigator to know their institutions policy regarding who can be an IND or IDE sponsor as well as who is authorized to sign contracts.

Financial Resources

The study budget should be clearly delineated from the outset. Institutions and drug/device or organizations providing financial support often have established budget templates that should be used. Organizations providing financial support generally assess "fair market value"; see the IISRA and ACRP position statements ([2010](#), [2013](#)) for a fuller explanation of fair market value. All costs should be described in a manner so that a researcher not directly involved in the study could understand what the costs represent. It is important to document which procedures may be deemed standard of care and not specific to the research activity. Procedures that are eligible for reimbursement should not be included in the study budget. Typical research costs to consider outlining in the budget are outlined in APPENDIX 4: Budget Checklist.

Any contracts with organizations providing financial support should include a section that clearly delineates when payments will be made. Payments can be made on a monthly or quarterly basis or they could be based on specific study milestones. Budget coordinators



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should consider when payments are being made, in addition to how much they are for. Additionally, the contract should prospectively delineate the rules for budget reconciliations in the event that the study ends early.

Once a study is ongoing, the cost of all supplies and labor should be calculated, tracked, and plotted against the allocated budget to determine any inconsistencies or needs for amending the study budget. In case of unforeseen delays or changes in the protocols, and based upon the likelihood of each scenario happening, the investigator should have budgeted for these risks. The allocated money held in reserve, should not be made accessible for regular procurement purposes, rather must only be available during extenuating circumstances.

Note that depending on your local transparency regulations, research payments may need to be disclosed publicly. In the United States, this is through the [CMS Open Payments Reporting website](#).

Facilities

The FDA defines research facilities as those where study activities will be conducted, and where clinical data will be generated or collected. This is meant to include facilities where subjects will be seen, and study procedures performed. Research facilities are not the same as clinical laboratory facilities, as the latter is defined as those meant to directly contribute or support the clinical study, as is the case of imaging centers or diagnostic or analytical labs supplying blood lab results for pharmacokinetic data ([ucm214282](#)). Facilities involved in hosting human subjects have to be certified that they can host human subjects in a way that protects their privacy, safety, and welfare. Facilities used for testing must have written standard operating procedures that are adequate to insure the quality and integrity of the data generated in the course of the study ([21 CFR 58.81](#)). As part of the standard operating procedures all analytical testing laboratories must have quality assurance and constant evaluation as part of written documentation ([21 CFR 58.35](#)). The investigator also needs to be cognizant of the all of the requirements of Good Laboratory Practices (GLP) that facilities must adhere to when hosting animals on its premises, which are meant to ensure humane treatment and proper documentation as part of pre-clinical studies ([21 CFR 58.90](#)).

Study Subjects

Perhaps the most important role of the investigator is to fully comprehend their responsibility in protecting the human subjects, and ensuring the integrity of the data from the clinical investigation. The IRB is instrumental in aiding the investigator in safeguarding the human subjects through vetting of all protocols. Prior to initiating the study, the FDA requires that the investigator submit information to the FDA on the health, demographic, and the number of study subjects to be recruited ([21 CFR 312.33](#)).



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A requisite risk and benefit assessment submission to the FDA must be completed based upon consultation with study subjects. This consultation consists of conversations with the subjects to understand their concerns and preferences regarding the study ([ucm451440](#)). If the risk profile of the trial changes or data collected during the study indicates a higher risk of adverse events, the new information needs to be promptly communicated to the IRB.

If there is a change to the IND, the FDA must be notified via an amendment if applicable under [21 CFR 312.30, 31](#). Also as part of that signed commitment in [Form FDA 1572](#), informed consent must be obtained from every subject in accordance with IRB approval ([ucm446695](#)). It is the sole responsibility of the PI to confirm that all subjects receiving intervention as part of the study are duly enrolled per FDA regulations ([21 CFR 312.61](#)). Investigators are obligated to convey changes to consented subjects so that a new informed consent can be obtained if the changes substantially affect the purpose of the study they are participating in, what the interventions will be, and what they can expect in terms of adverse effects ([21 CFR 50.20](#)).

Adverse events for all subjects must be carefully collected, and may need to be submitted to the IRB, FDA, the drug or device manufacturer, and/or the study's data safety monitoring board (DSMB) as part of safety monitoring ([ucm127073](#)) ([21 CFR 312.33](#)). The Sponsor-Investigator will need document the type of event (preferably according to [Medra](#) terminology), the seriousness ([E2B](#)), the relatedness ([CDASH](#)), and the expectedness per the prescribing information and/or Investigator's Brochure. In cases of lethal or life threatening adverse events in subjects, the FDA currently mandates that those events be filed on a [MedWatch](#) form within 15 days ([ucm446695](#)) ([21 CFR 312.32](#)). Only adverse events that are considered unexpected, serious, or pose significant implications for overall study need to be reported to the FDA and IRB for both INDs and IDEs. Adverse events reporting requirements for IRBs and drug or device manufacturers vary by organization, so pay special attention to these criteria ([ucm 079753](#)). Also pay special attention to any local country reporting requirements if your study has participating sites in other countries.

Certain subpopulations of study subjects require additional protections and/or follow different regulations, and as such it is the responsibility of the investigator to be able to identify who these populations are ([21 CFR 50 to 56](#)). In the rare occurrence that during the course of the study informed consent cannot be obtained (i.e., a subject is in a life threatening situation and is unconscious), contingency plans should be in place so relevant staff can immediately respond



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to the situation in accordance with regulations ([21 CFR 50.23](#)). For any study in which the subject population is unable to give consent, an IND must be submitted, even if under other circumstances the study would be considered IND-exempt.

When collecting information on the study subjects care needs to be taken to guarantee compliance with [45 CFR Part 160 of HIPAA \(21 CFR 312.57, 21 CFR 812.140\)](#). The HIPAA Privacy Rule establishes national standards to protect the individuals' medical records as well as other personal health information (PHI). The investigator's responsibility includes safeguarding PHI, and prior to conducting the study should consider options for protecting the data (i.e., waiver authorization, de-identification). If there is an accidental disclosure of PHI, all study staff have a duty to report the disclosure, and understand the procedures to do so.

Recruiting and Screening Capabilities

The FDA requires that the IRB review the methods and materials that investigators propose to use to recruit subjects for the trial. This requirement falls under ([21 CFR 56.107\(a\) and 56.111](#)), which is intended to safeguard the rights and welfare of the subjects. As part of the collaboration required between the IRB and sponsor, it is the responsibility of both parties to ensure that all direct advertising contain the following information: criteria selection, commitment requirements, purpose of the study, and contact information of relevant personnel to properly inform prospective study subjects about the research ([ucm126428](#)).

The FDA and IRB assess the materials to ensure they do not promise favorable outcomes beyond what is contained in the protocol, does not contain language indicating that the FDA or IRB has approved the research, does not contain exculpatory language and language that implies the test product is superior or equivalent to any other product, and is free of language that could mislead patients.

Under FDA guidelines the IRB must review communications for health professionals. Generally speaking, the FDA believes recruitment advertisement should be limited to information that is needed for prospective treatment subjects to determine their eligibility and interest. Investigators should be aware that the IRB and FDA will steer you away from using the terms "free medical treatment," when the wording would be more accurately listed as "no charge for treatment" while enrolled in the study. Additionally, all advertisements must be careful not to overly emphasize compensation as a means to attract subjects ([21 CFR 812.7\(d\)](#)).



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Recruitment Considerations

The information provided in this section is meant to guide the investigator in recruitment of study subjects, and is by no means intended to serve as regulatory advice. In order to keep a study on a strict timeline, and to maintain statistically useful data, the investigator needs to recruit reliable study subjects. Factors to consider include socioeconomics, transportation, inclusion of professional research subjects, and overall subject reliability.

Depending upon the location of the study site(s) as well as product being studied, there will be a wide range of socioeconomic subjects. This is important to understand as each group of prospective subjects will have different needs. For instance, due to the wide prevalence of low health information comprehension, it is considered best practice to make sure any information conveyed to study subjects is no higher than a 4th or 5th grade level. There are numerous online tools to assist with determining the grade level of a document and some word processors, such as [Microsoft Office](#), incorporate this into their software.

Additionally, subjects who are economically disadvantaged may not have the means to afford them the ability to take time off of work to take part in the study, or for that matter the ability to afford transportation to study sites. Thus, the investigator needs to be aware of these situations when determining compensation to ensure steady and reliable participation and follow-up. Prior to enrollment into the study, all subjects should be screened on their ability to obtain adequate transportation, and if this is not possible sponsors may need to either provide alternative transportation, or consider a travel stipend. For US studies that require long-term survival follow-up, the [CDC's National Death Index](#) is a helpful tool, especially when subjects aren't able to continue in-office assessments.

Contingency plans should be discussed in protocols for addressing communication barriers, especially those arising from use of multiple languages across the study sites. This is very important, as the use of translators should then be factored in budgetary documents.

Inclusion of professional research subjects should be discussed between the study coordinator and sponsor ahead of time. If the decision is made to include these subjects in the study, their backgrounds need to be properly vetted to prevent any possible bias that could negatively affect the integrity of the data. The reason these subjects need to be properly vetted, is that they may be enrolled in multiple studies, which could inadvertently result in adverse effects from drug-drug interactions.



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Conflicts of Interest

The FDA requires that all the clinical investigators who have helped out on the study as well as all full-time and part-time employees of the sponsor provide disclosure of conflicts of interest (*ucm341008*) (*21 CFR 54.4*). All disclosures need to be disclosed prior to the initiation of the study (*21 CFR 312.53(c)*, *812.20(b)(5)* and *812.43(c)*). Records on the sponsor-investigator's financial interests and arrangements have to be maintained for at least 2 years after an application has been approved, and must be made accessible to the FDA in cases of both INDs and IDEs (*21 CFR 312.54, 57*). Technically, this information is not required in the IND/IDE application, however, the information is required before the clinical investigator can participate in the trial.

For clinical investigators who are not full-time or part-time employees of a drug or device manufacturer, the applicant must provide either certification, using *Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators)*, or *Form FDA 3455 (Disclosure: Financial Interest and Arrangements of Clinical Investigators)*, which documents financial conflicts of interest. If, after due diligence, the sponsor is unable to obtain the required information, they may certify that they acted with due diligence, but must provide in writing a reason for an inability to obtain the information (*21 CFR 54.4*). For sub-investigators who are not full-time employees of the sponsor-investigator, financial information must be updated and certified for one year following the completion of the study.

The financial interests and agreements that must be disclosed to the FDA include the following (*21 CFR 54.4(a)(3)*, *ucm341008*):

1. Any compensation made to the investigator by any sponsor of the covered clinical study in which the value of compensation could be affected by study outcome.
2. A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright or licensing agreement.
3. Any equity interest in any sponsor of the covered clinical study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.
4. Any equity interest in any sponsor of the covered study if the sponsor is a publicly held company and the interest exceeds \$50,000 in value. The requirement applies



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to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

5. Significant payments of other sorts, or payments that have a cumulative monetary value of \$25,000 or more and are made by any sponsor of a covered study to the investigator or the investigator's institution during the time the clinical investigator is carrying out the study and for one year following completion of the study. This would include payments that support activities of the investigator (e.g., a grant to the investigator or to the institution to fund the investigator's ongoing research or compensation in the form of equipment), exclusive of the costs of conducting the clinical study or other clinical studies, or to provide other reimbursements such as retainers for ongoing consultation or honoraria.

In determining whether the financial disclosure presents a potential conflict of interest, the FDA will consider study design, study sites, investigators, and replication of data. If there is a question regarding the validity of data related to a conflict of interest, the FDA may take action ranging from inspections to requesting independent verification of the data in question or even elimination of the data in question for application purposes. Even if the institution of the investigator finds no potential conflicts of interest, the FDA reserves the right to make their own assessment. Investigators need to be cognizant not only about their own financial interests, but also their spouses and dependent family members as the FDA can consider these sources of potential conflicts of interests ([21 CFR 312.54](#)).

Investigators who are also sponsors must pay particular attention to management of conflicts of interest with regard to the study. While it may be virtually impossible to eliminate all conflicts, all attempts should be made to minimize them. Possible strategies to manage conflicts include reduction of financial interests, disclosure of all financial interest to study subjects, additional oversight of research by external party, modification of roles to separate financial decisions from clinical decisions, and/or elimination of all financial interests. Any newly developed conflict of interest should be immediately declared to all appropriate parties to not only comply with regulations, but to avoid any potential situations of perceived unethical behavior. All conflicts of interest by all parties should be declared as completely as possible before the initiation of the trial to protect the integrity of the study. Investigators should be conscious of the fact that even if there are no financial conflicts of interest, they may harbor scientific biases that are regarded in a similar light as financial interests.



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Confidentiality and Disclosures

Study staff members should be aware of the roles and responsibilities in the study protocol, and all members should sign contracts promising to carry out those roles to guarantee the integrity of the study. These contracts should always include language surrounding confidentiality. Study results should never be promoted or “leaked” before they are ready for publication or presentation, and staff should understand how to utilize all safeguards. Additionally, if a company provides product or financial support, they typically will reserve the right to see results prior to public disclosure. Premature disclosure of study results can threaten acceptance to a peer-reviewed journal and has the potential to result in the media shaping public perception based upon incomplete or biased information. Therefore, details of the study should be kept as simple as possible if information is going to be released to the public or media outlets in order to avoid miscommunication. If the study impact is wide reaching, the investigator may want to consider hiring a dedicated public relations staff member to craft the message heard by media and public.

Intellectual Property Considerations

Depending upon the study, there may be intellectual property (IP) implications, and it falls on the shoulders of the investigator to understand these implications, and convey them to the staff members. This should be given early consideration, to enable legal counsel to put a clause in the contracts stating the implications of unauthorized transfer of sensitive intellectual property information. Investigators at academic institutions need to consult with the appropriate department and their technology transfer office (TTO) to determine who will own any intellectual property generated from the study. For a detailed explanation of this and other contractual considerations, see the ACRP’s White Paper on [Contracting for Investigator Initiated Sponsored Research](#).

Inspections

It is imperative that the study investigator familiarizes themselves and comprehends the criteria for conduction of announced and unannounced FDA inspections ([ucm126553](#)) (21 CFR 312.68, 812.145). The FDA has different criteria for investigational drugs, biologics, and medical devices, thus, the investigator must be aware of the classification of their study ([ucm126553](#)) (21 CFR 312.120, 814.15). Clinical investigators who are conducting FDA regulated clinical investigations are required to allow FDA inspectors to access, copy, and verify any records made by the clinical investigator with regards to the subjects’ case histories. The



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purpose of these inspections is to ensure the validity of the data and protection of subjects. Inspections may be initiated to verify accuracy and reliability of data, upon termination of a clinical site, at the request of a FDA review division, respond to complaints against study sites, and investigate specific classes of investigational products that the FDA has deemed as special interest (*21 CFR 812.140(d)*). At the end of the inspection, the FDA will conduct an exit interview with the investigator to discuss the findings, and if any deficiencies were found the inspector will issue a written *Form FDA 483 (Inspectional Observations)*.

Common deficiencies that have been observed by FDA investigators have included: failure to follow the approved protocol, inadequate recordkeeping, inadequate accountability for the investigational product, and poor protection of subjects (particularly those related to informed consent issues) (*21 CFR 312.66*). The FDA posts warning letters publicly on their website and it is useful to review a few of these letters to understand the rationale behind decisions in order to avoid the same pitfalls. To ensure an efficient response to any infractions or violations, the investigator should become familiar with the appeals process.

Investigators should be aware of information that the FDA investigators are not allowed access to under normal conditions. To properly prepare for inspections, it should be communicated to all study staff who the inspectors can talk with, what information they can access, and staff members should be coached on how to respond to questioning by the inspectors.

It is recommended that a standard operating process (SOP) be developed to assure that the right things are done consistently by the right people in the right way. All personnel involved in the research shall be trained. The training shall be documented.

Facility Considerations

Any facility involved in hosting human subjects has to be certified that they can host subjects in a manner that ensures their privacy, safety, and welfare are maintained throughout the entire course of the study. Part of this certification involves the investigator guaranteeing that all facilities have appropriately trained personnel.

All facilities involved in the trial have to be documented in *Form FDA 1572 (21 CFR 812.35)*. Separate records must be maintained at each site detailing how the data was collected, and the how the analyses was conducted. If for any reason a facility can no longer maintain or store the



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records, then the records must be transferred to the sponsor-investigator for secure storage ([21 CFR 58.195](#)).

If the study requires the use of controlled substance as defined by the FDA, the facility must be registered with the DEA ([21 CFR 1300 & 1301](#)). Additionally, the investigator shall take adequate precautions, including secure storage of the investigational drug, as well as proper documentation of usage and disposal of the product ([21 CFR 312.69](#)).

Under [21 CFR 58](#), non-clinical methods used for collection of pre-clinical data should be governed under Good Laboratory Practices (GLP). GLPs are intended to promote the quality and validity of the test data, just as Good Manufacturing Practices (GMPs) are aimed at ensuring quality production materials and products.

Drug Supply

It is important to make sure that you have adequate facilities to store any interventional material, especially if investigational medicinal product is included in the study design. Investigators should determine whether the supplied product will require that an investigational or research pharmacy to be involved. Additionally, for multi-center investigations it is important to have a clear understanding of how drug will be distributed to participating sites, either direct from the manufacturer, from a contracted distributor, or from a local pharmacy. Logs must be maintained to account for the distribution of all product and provide the means to facilitate recoveries or recalls, if necessary. The sponsor-investigator should also consider whether unused or expired product may be destroyed on-site or whether it will need to be returned for destruction at a central location.

Study Data and Data Retention

As part of ensuring the integrity of the study data, investigators are required to employ procedures and controls designed to safeguard confidentiality of PHI when appropriate; and have barriers preventing manipulation of signed data. Access to data is recommended to be limited to authorized personnel to prevent unauthorized modifications to the data. Each study staff member should be assigned a unique electronic signature that employs two distinct forms of ID verification. Therefore, the investigator should examine the electronic systems they plan on using in the study to confirm that they are able to meet the minimum requirements of the FDA regarding electronic storage of study data ([21 CFR 58.190](#)). In order to understand the requirements for each site, the investigator must first know whether the site is operating under an open or closed system. Per the FDA, a closed system is one in which the person responsible



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for the content controls the access. Likewise, if the person responsible for the content does not control access, then the system is referred to as open since the records can be modified without permission from the investigator (*21 CFR Part 11*). Open systems and closed systems have different requirements due to their nature of security associated with each.

The FDA has storage duration requirements that are different for the types of data, and to preserve long-term access to the records the investigators need to be familiar with FDA compatible technology (*21 CFR 58.190*). Typically, the duration of storage is directly related to whether the data is non-clinical or clinical in nature.

Multi-Site Responsibility

A trial may include multiple sites for human subject testing, however the sponsor-investigator needs to understand that they assume sponsor oversight responsibility across all sites. For those investigators who have participated in trials sponsored by a pharmaceutical or device manufacturer, investigator-sponsored trials require additional oversight that the manufacturer typically provides on their own trials. For example, the sponsor-investigator is responsible for reporting serious adverse events across all sites to the FDA, and for ensuring that suspected unexpected serious adverse reactions (SUSARs) are reported to each of the respective IRBs. The sponsor-investigator reserves the right to terminate or suspend operations at individual sites as they see fit, however the investigator must document the reason.



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Foreign Site

Clinical research has become increasingly global, which the FDA has recognized by issuing guidance related to the conduction of multinational clinical studies under an IND as well as those meant to support an IND ([ucm294729](#)). Alternatively, sponsors can elect to rely solely on foreign clinical data to support an IND application. The investigator needs to understand that the FDA will not accept as support for an IND or application for marketing approval any study that does not meet the conditions of [21 CFR 312.120](#), but they will assess the study data to aid in the determination of safety of the product. Good Clinical Practices (GCP) needed to meet [21 CFR 312.120](#) are defined by the FDA. If the study is conducted under a FDA IND, all requirements of domestic INDs must be met, unless otherwise waived by the FDA. Location of information required by [21 CFR 312.120](#) must clearly delineate in the IND submission to facilitate a timely review of the application.

Conclusion

Investigator Initiated Sponsored Research is an important vehicle for evidence generation, however regulations and guidelines are not always clear or straightforward when it comes to this type of research. Investigators wishing to act as sponsor for their own trials need to be familiar with both investigator and sponsor responsibilities and have the institutional infrastructure to support the trial for other activities, such as required regulatory filings. Without appropriate oversight, IISRs can pose large legal and regulatory risks to the investigator and their institution. However, well-executed programs may allow an investigator to have access to novel agents, bring additional research funding to the institution, produce valuable intellectual property, result in important publications, and most importantly, bring medicines to the patients that need them most.



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APPENDIX 1: References

Guidance Documents:

UCM 071717. *Guidance for Industry. IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer.*

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM071717.pdf>

UCM 079753. *Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse Event Reporting to IRBs — Improving Human Subject Protection.* <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm079753.pdf>

UCM 126418. *Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors. Significant Risk and Nonsignificant Risk Medical Device Studies.*

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm126418.pdf>

UCM 126425. *Sponsor - Investigator - IRB Interrelationship - Information Sheet. Guidance for Institutional Review Boards and Clinical Investigators.*

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126425.htm>

UCM 126428. *Recruiting Study Subjects - Information Sheet. Guidance for Institutional Review Boards and Clinical Investigators.*

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm>

UCM 126553. *Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors. FDA Inspections of Clinical Investigators.* <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm126553.pdf>

UCM 126997. *Guidance for Industry and Clinical Investigators. The Use of Clinical Holds Following Clinical Investigator Misconduct.* <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm126997.pdf>

UCM 127067. *Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors.*

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf>

UCM 127073. *Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data Monitoring Committees.*

<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm127073.pdf>

UCM 187772. *Guidance for Industry: Investigator Responsibilities-Protecting the Rights, Safety, and Welfare of Study Subjects.*

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM187772.pdf>

UCM 201790. *Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics.*

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm201790.pdf>

UCM 214008. *Information Sheet Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors Clinical Investigator Administrative Actions – Disqualification.*



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<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm214008.pdf>

UCM 214282. *Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs.*

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm214282.pdf>

UCM 229175. *Guidance for Clinical Investigators, Sponsors, and IRBs. Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND.*

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm229175.pdf>

UCM 269919. *Guidance for Industry: Oversight of Clinical Investigations-A Risk Based Approach to Monitoring.*

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf>

UCM 294729. *Guidance for Industry and Staff: FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND. Frequently Asked Questions.*

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf>

UCM 341008. *Guidance for Clinical Investigators, Industry, and FDA Staff. Financial Disclosure by Clinical Investigators.*

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm341008.pdf>

UCM 366335. *IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed.*

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm366335.htm>

UCM 389154. *Humanitarian Device Exemption (HDE): Questions and Answers - Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff.*

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm389154.htm#review>

UCM 392728. *Live Case Presentations During Investigational Device Exemption (IDE) Clinical Trials - Draft Guidance for Institutional Review Boards, Industry, Investigators, and Food and Drug Administration Staff.*

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm392728.htm>

UCM 405622. *The Drug Development Process. Step 3: Clinical Research.*

<http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm>

UCM 446695. *Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators- Guidance for Industry.*

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm446695.pdf>

UCM 451440. *Factors to Consider When Making 2 Benefit-Risk Determinations for 3 Medical Device Investigational Device 4 Exemptions (IDEs) 5 6 7 Draft Guidance for IDE Sponsors, 8 Sponsor-Investigators and 9 Food and Drug Administration Staff.*



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<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm451440.pdf>

Regulatory

21 CFR 11. Electronic Records; Electronic Signatures.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11>

21 CFR 25. Environmental Impact Considerations.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=25>

21 CFR 50. Protection of Human Subjects.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=50>

21 CFR 54. Financial Disclosure by Clinical Investigators.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=54>

21 CFR 56. Institutional Review Boards.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=56>

21 CFR 58. Good Laboratory Practice for Nonclinical Laboratory Studies.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=58>

21 CFR 60. Patent Term Restoration.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=60>

21 CFR 312. Investigational New Drug Application.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=312>

21 CFR 812. Investigational Device Exemptions.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812>

21 CFR 814. Premarket Approval of Medical Devices.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=814>

21 CFR 860. Medical Device Classification Procedures.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=860>

21 CFR 1300. Definitions.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=1300>

21 CFR 1301. Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=1301>

45 CFR 160. General Administrative Requirements. http://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title45/45cfr160_main_02.tpl



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APPENDIX 2: Definitions and Abbreviations

Term	Definition
Investigator Initiated Sponsored Research (IISR)	Research where a Sponsor-Investigator independently proposes research and requests support from the manufacturer in the forms of funding and/or product. The Investigator or Institution serves as the study Sponsor and assumes responsibility for designing the study, directing the administration of study drug, ensuring compliance with all local laws and regulatory requirements, and analyzing and communicating any study results.
Sponsor-Investigator (S-I)	An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (i.e., it does not include a corporation or an agency). The obligations of a Sponsor-Investigator include both those of a Sponsor and those of an Investigator.
Investigator	An individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team
Sponsor	A person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.
Adverse Event (Drug)	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
Biologic	Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. In contrast to most drugs that are chemically synthesized and their structure is



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	known, most biologics are complex mixtures that are not easily identified or characterized.
Center for Biologics Evaluation and Research (CBER)	Branch of the U.S. Food and Drug Administration that regulates biologics. Monoclonal antibodies and other therapeutic proteins are regulated by CDER.
Center for Devices and Radiological Health (CDRH)	Branch of the U.S. Food and Drug Administration responsible for the premarket approval of all medical devices, as well as overseeing the manufacturing, performance and safety of these devices.
Center for Drug Evaluation and Research (CDER)	Branch of the U.S. Food and Drug Administration that regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs.
Chemistry, Manufacturing and Controls (CMC)	The process by which a drug or biologic is made.
Code of Federal Regulations (CFR)	The general and permanent rules and regulations (sometimes called administrative law) published in the Federal Register by the executive departments and agencies of the federal government of the United States. Food and Drugs are outlined in Title 21.
Cross-Reference Letter	The letter of cross-reference authorization allows the FDA to review the specified content in the referenced IND, NDA, or BLA and to rely on its previous reviews of information already submitted in the commercial sponsor's application, so that the sponsor-investigator does not need to provide that information again (e.g., CMC, nonclinical, and previous human experience data). Sponsor-investigators should note that although a letter of cross-reference authorization allows the FDA to refer to the commercial sponsor's content, it does not give sponsor-investigators the right to directly access and read confidential material contained in the referenced IND, NDA, or BLA.
Data Safety Monitoring Board (DSMB)	An independent group of experts who monitor patient safety and treatment efficacy data while a clinical trial is ongoing.
Device	Section 201(h) of the FD&C Act (21 USC 321(h)) provides that the term "device" means: ... an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--



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	<p>(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,</p> <p>(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or</p> <p>(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.</p>
Drug	<p>Section 201(g) of the FD&C Act (21 USC 321(g)) provides that the term "drug" means:</p> <p>(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C).</p>
Fair Market Value (FMV)	<p>The fair market value is the price at which the property would change hands between a willing buyer and a willing seller, neither being under any compulsion to buy or to sell and both having reasonable knowledge of relevant facts. The fair market value of a particular item of property includible in the decedent's gross estate is not to be determined by a forced sale price. Nor is the fair market value of an item of property to be determined by the sale price of the item in a market other than that in which such item is most commonly sold to the public, taking into account the location of the item wherever appropriate. Regulation §20.2031-1.</p>
Food and Drug Administration (FDA)	<p>A federal agency of the United States Department of Health and Human Services, responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed and veterinary products.</p>



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<p>Good X Practice (GXP)</p>	<p>An international quality standard that is provided by the International Council for Harmonization. The most common are good clinical (GCP), laboratory (GLP), manufacturing (GMP) practices. GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.</p>
<p>Health Care Professional (HCP)</p>	<p>A health professional within a branches of health care, including but not limited to medicine, surgery, dentistry, midwifery, pharmacy, psychology, nursing or allied health professions.</p>
<p>Health Insurance Portability and Accountability Act (HIPAA)</p>	<p>A U.S. law designed to provide privacy standards to protect patients' medical records and other health information provided to health plans, doctors, hospitals and other health care providers.</p>
<p>Humanitarian Use Device (HUD)</p>	<p>A device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.</p>
<p>Humanitarian Device Exemption (HDE)</p>	<p>Similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA.</p>
<p>Investigational Device Exemption (IDE)</p>	<p>IDE refers to the regulations under 21 CFR 812. An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and all the requirements under 21 CFR 812 are met.</p>
<p>Informed Consent Form (ICF)</p>	<p>The form which documents that the patient was informed of and understands the purpose, benefits, and potential risks of a medical or surgical intervention, including clinical trials, and then agrees to receive the treatment or participate in the trial.</p>
<p>Institutional Review Board (IRB)</p>	<p>In the U.S., the Institutional Review Board (IRB) is a board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights, safety, and welfare of human subjects. The IRB should be established, operated, and function in conformance with 21 CFR 56. These are also known as ethics committee (EC) in Europe and Research Ethics Board (REB) in Canada.</p>



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Intellectual Property (IP)	Refers to creations of the mind, such as inventions; literary and artistic works; designs; and symbols, names and images used in commerce. In medical research, any resulting IP is owned by the Sponsor unless there is a contractual agreement which states otherwise.
Investigational New Drug Application (IND)	In the U.S., an Investigational New Drug Application (IND) is a request for Food and Drug Administration (FDA) authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved new drug application. The application is completed on Form FDA 1571. In Europe, the equivalent is called a Clinical Trial Application (CTA).
Medical Science Liaison (MSL)	A healthcare consulting professional who is employed by pharmaceutical, biotechnology, medical device, and managed care companies to inform other health care professionals of the scientific and medical aspects of their products. These are sometimes referred to as Clinical Science Liaison (CSL).
New Drug Application (NDA)	The vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the United States. The purpose of a NDA is to provide enough information to determine whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
Non-Significant Risk (Device)	Investigational device that does not meet significant risk device requirements.
On-label	Research product is used in the study according to its description in its approved marketed label. The label identifies the disease (indication), population, dose, duration, and other specific information. This is one of the requirements if an investigator would like an IND or IDE exemption.
Off-label	Research product is not used within the approved marketed label. A regulatory filing and approval may be required by the Sponsor-Investigator or Sponsor before initiating a clinical study.
Package Insert	A package insert is a document provided along with a prescription or over-the-counter medication to provide additional information about that drug. This is also sometimes referred to as Prescribing Information.
Protected Health Information (PHI)	Under U.S. law, any information about health status, provision of health care, or payment for health care that is created or collected by



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	a "Covered Entity" (or a Business Associate of a Covered Entity), and can be linked to a specific individual.
Patient Protection and Affordable Care Act	Under a part of this act, the Centers for Medicare and Medicaid Services were charged with developing a portal where transfers of value from applicable manufacturers and group purchasing organizations (GPOs) to physicians and hospitals are made publicly available.
Premarket Approval (PMA)	The FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.
Regulatory Authority	Bodies having the power to regulate. In the ICH GCP guideline, the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.
Research Agreement	A legal document that describes provision of funding, material support or both material support for a clinical or preclinical study and outlines obligations of all parties. Colloquially referred to as a study contract.
Risk Determination (Device)	The risk determination of a device is based on the proposed use of a device in an investigation, and not on the device alone. SR studies present a potential for serious risk to the health, safety, or welfare of a subject. IRBs should consider the potential harm the procedure could cause as well as the potential harm caused by the device.
Serious Adverse Event (SAE)	Any untoward medical occurrence that: <ul style="list-style-type: none"> • results in death, • is life-threatening • requires inpatient hospitalization or causes prolongation of existing hospitalization • results in persistent or significant disability/incapacity, • is a congenital anomaly/birth defect, or • requires intervention to prevent permanent impairment or damage



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<p>Suspected Unexpected Serious Adverse Reactions (SUSAR)</p>	<p>SAEs judged to be both:</p> <ul style="list-style-type: none"> • related to drug therapy • not described in the package insert or IB, as applicable <p>Sponsor-Investigators are required to report SUSARs to their local regulatory authority.</p>
<p>Significant Risk (SR)</p>	<p>Significant risk device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject; (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to a subject.</p>
<p>Standard of Care (SOC)</p>	<p>A diagnostic and treatment which the average, prudent provider in a given community would practice for a certain type of patient, illness, or clinical circumstance.</p>
<p>Substantial Evidence (Drug)</p>	<p>“Substantial evidence” means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.” <i>(Food Drug and Cosmetic Act 21 USC § 355(d))</i></p>
<p>Trial Master File (TMF)</p>	<p>The trial master file consists of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated. Those documents shall show whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice and with the applicable requirements. There is a Steering Committee of multiple companies and contract research organizations which publishes TMF Reference Models.</p>
<p>Unanticipated Adverse Effect (Device)</p>	<p>Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature,</p>



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	severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Valid Scientific Evidence (Device)	“Valid scientific evidence” is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. <i>(21 CFR 860.7(c)(2)).</i>



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APPENDIX 3: Staff and Site Checklists

Principal Investigator Considerations	
<input type="checkbox"/>	Experience & knowledge (clinical & regulatory) necessary to be a sponsor-investigator
<input type="checkbox"/>	Desire to take on regulatory responsibilities and understanding of FDA regulations
<input type="checkbox"/>	Familiarity with procedures for announced/unannounced FDA inspections
<input type="checkbox"/>	Experience facilitating IRB reviews
<input type="checkbox"/>	Thorough understanding of the investigational drug or device's risks and benefits
<input type="checkbox"/>	Not currently debarred or have any violations that would be of concern
<input type="checkbox"/>	Ability to plan for any long-term aspects of the study
<input type="checkbox"/>	Ability to identify study staff and provide necessary training
<input type="checkbox"/>	Available resources (facilities, equipment, administration)
<input type="checkbox"/>	Able to supervise the conduct of the study
<input type="checkbox"/>	Available tools for recruiting & screening
<input type="checkbox"/>	Experience consenting patient population, including any special needs for minors, etc.
<input type="checkbox"/>	Reputation as a thought leader
<input type="checkbox"/>	Record of quality research that has been published in credible, peer-reviewed journals
Study Staff Considerations	
<input type="checkbox"/>	Identify a study coordinator with pertinent knowledge and experience
<input type="checkbox"/>	Recruit study staff
<input type="checkbox"/>	Consider number of staff needed and required experience
<input type="checkbox"/>	Identify trainings, competencies, and licensure required for the study scope
<input type="checkbox"/>	Plan for staff turnover
Legal Considerations	
<input type="checkbox"/>	Establish confidentiality agreements
<input type="checkbox"/>	Identify required contracts to start/maintain/end project
<input type="checkbox"/>	Ensure adequate contracts and/or legal staff to negotiate agreements
<input type="checkbox"/>	Obtain intellectual property rights
<input type="checkbox"/>	Identify conflicts of interest
Administration	
<input type="checkbox"/>	Identify requirements for grant management
<input type="checkbox"/>	Ensure adequate regulatory staff to make any necessary submissions to the FDA and clinicaltrials.gov
<input type="checkbox"/>	Staff to support protocol writing (e.g. research nurses, biostatistics, laboratory samples)
<input type="checkbox"/>	IRB: be aware of review schedule and plan accordingly



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Facility Considerations

Research facilities are defined as places where any study activities are done and clinical data are generated and collected, especially places involving study subjects. Any facility used in a study should have the requisite structure, space, location, equipment, staff and general ability to facilitate the study competently. Any facility involved in hosting human subjects have to be certified that they can host those subjects in a way that protects their privacy, safety, and welfare.

- Identify appropriate facility for the study
- Must have adequate/secure storage
- Establish study drug/device use log
- Develop study records (separate from other studies)
- Follow regulations for electronic systems (21 CFR 11)

Laboratory

Clinical laboratory facilities are defined as places using analytical and testing capabilities to support a clinical study

- Appropriate certification to handle samples
- Written SOPs for all procedures
- Sufficient capabilities available (including equipment and staff)
- Consider if samples will be tested in-house vs. sent out
- The hours a lab may be open should be negotiated and determined beforehand between the lab staff involved and the investigator to comply with the study protocol
- Monitor and document storage temperature
- Determine if specialized diagnostic equipment is required

Pharmacy/Clinic

- Ensure product is stored in temperature appropriate settings and there is adequate space
- Identify means for disposal or return of any unused product

Protocol Considerations

- Evaluate experience with similar protocols (design & drug/device)
- Subject availability required by the protocol
- Other similar studies (in-house and external)
- Evaluate facility appropriateness
- Evaluate staff availability



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Regulatory Compliance Considerations	
<input type="checkbox"/>	Previous inspection history and outcomes (investigator/facility/IRB)
<input type="checkbox"/>	Previous FDA warning letters (investigator/facility/IRB)
<input type="checkbox"/>	Previous disqualification/restrictions (investigators/facility)
<input type="checkbox"/>	FDA debarment list (investigator/facility)

Demographic Considerations	
<input type="checkbox"/>	Study population socio-economics and impact on study participation
<input type="checkbox"/>	Subject's access to transportation
<input type="checkbox"/>	Reliability of study subjects
<input type="checkbox"/>	Awareness of professional research subjects
<input type="checkbox"/>	Subject's barriers to follow-up

Risk Management Considerations	
<input type="checkbox"/>	Consider public perception
<input type="checkbox"/>	Consider possible media interest and impacts
<input type="checkbox"/>	Evaluate perceived value
IRB Considerations	
<input type="checkbox"/>	Compliance with 21 CFR 50 (human subject protection)
<input type="checkbox"/>	Compliance with 21 CFR 54 (investigator financial disclosure)
<input type="checkbox"/>	Compliance with 21 CFR 56 (IRB)
<input type="checkbox"/>	Compliance with 45 CFR 46 (protection of human subjects), Federalwide Assurance (FWA) accepted by the Office for Human Research Protections (OHRP)
<input type="checkbox"/>	Consider frequency of meetings, review time, and Association for the Accreditation of Human Research Protection Programs (AAHRPP) accreditation
<input type="checkbox"/>	Stipulations associated with approval/no approval
<input type="checkbox"/>	Identify special requirements for certain populations (vulnerable, pregnant, pediatric, and prisoner)
<input type="checkbox"/>	Need for special reviews (radiation, biosafety, etc.)
<input type="checkbox"/>	Consider the type of IRB that will be used (institutional/academic or commercial/for-profit)



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Study Documentation Checklist	
<input type="checkbox"/>	CVs and Medical License of all participating investigators
<input type="checkbox"/>	Roles and Responsibilities list for all study staff
<input type="checkbox"/>	Forms FDA 1571 & 1572 or written attestation of exemption criteria
<input type="checkbox"/>	Monitoring Plan
<input type="checkbox"/>	Research agreements with any organizations providing support
<input type="checkbox"/>	Consent Form
<input type="checkbox"/>	Protocol
<input type="checkbox"/>	Confirmations and Disclaimers of Financial Conflicts of Interest for all participating investigators
<input type="checkbox"/>	Laboratory Manual (if applicable)
<input type="checkbox"/>	Investigator's Brochure and/or Prescribing Information
<input type="checkbox"/>	Written guidelines for safety processing and reporting both SAEs from the trial investigators, and SUSARs distributed from the manufacturer
<input type="checkbox"/>	Statistical Analysis Plan (SAP)
<input type="checkbox"/>	Public posting of trial on clinicaltrials.gov
<input type="checkbox"/>	Written timelines of estimated study progress
<input type="checkbox"/>	List of any special certifications required to perform study activities, including any applicable expiration dates
<input type="checkbox"/>	Recruitment expectations
<input type="checkbox"/>	Advertising material for patient recruitment (if applicable)
<input type="checkbox"/>	System for storing and/or analyzing study data



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APPENDIX 4: Budget Checklist

It is important to have an estimate of the anticipated trial costs, as well as a clear understanding of when financial payments will need to be made over the duration of the trial. It should be clearly outlined in the budget documentation which activities are considered standard of care and which activities are directly related to the research and need to be covered through a mechanism other than reimbursement.

If funding support is requested through a drug or device manufacturer, the requested budget will be assessed to determine Fair Market Value. It is customary for manufacturers to deny the purchase of capital equipment (an alternative is leasing equipment), ordinary operating expenses, or costs considered standard of care.

Activities and Fees to Consider within the Study Budget	
<input type="checkbox"/>	Protocol Writing
<input type="checkbox"/>	Regulatory submission and review fees
<input type="checkbox"/>	Institutional start-up fees, such as scientific reviews, pharmacy set-up, etc.
<input type="checkbox"/>	Staff training costs
<input type="checkbox"/>	Travel for required monitoring visits
<input type="checkbox"/>	Safety Reporting
<input type="checkbox"/>	Storage costs, such as pharmacy or documentation for the trial master file
<input type="checkbox"/>	Translation and/or interpreter costs
<input type="checkbox"/>	Patient-level procedural or correlative costs
<input type="checkbox"/>	Travel stipends for patients
<input type="checkbox"/>	Travel stipends for study staff to attend medical conferences
<input type="checkbox"/>	Annual fees and/or renewals, such as IRB, pharmacy, and updates to the IND
<input type="checkbox"/>	Consultant fees for items such as biostatistical analyses
<input type="checkbox"/>	Manuscript development for publications
<input type="checkbox"/>	Overhead costs