



# American College of Foot and Ankle Surgeons™

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## Getting Started in Research in Your Private Practice

Physicians interested in developing their careers and furthering the interests of their patients may choose to do so by becoming clinical researchers. Becoming a researcher is a daunting challenge, so every would-be researcher should be fully aware of the benefits, risks and responsibilities of conducting clinical research.

### Part 1: Why do research?

There are numerous benefits to adding a clinical research module to your practice:

1. For new practitioners, being involved in cutting-edge research is a valuable marketing tool for recruiting new patients:
  - It helps compensate for a perceived “lack of experience” by demonstrating a progressive attitude toward treatment;
  - Signaling an interest in research alerts referring physicians of the potential for alternative treatment options for their patients;
  - Patients will typically continue treatments with their physician once the trial ends.
2. For experienced practitioners, clinical research:
  - provides access to cutting edge technology, and the opportunity to try something new (and hopefully better) than what traditional protocols have stipulated;
  - offers advanced treatments in a highly controlled, scientific environment, typically with considerable support in the form of blood studies and more frequent and detailed observations than you may normally perform;
  - provides treatment that is usually offered at no cost to patients;
  - offers significant continuing educational opportunities;
  - demands a more comprehensive, detailed evaluation of patient response to a given treatment; and
  - usually adds additional revenue to a practitioner’s bottom line.
3. For residence directors and residents alike, clinical trials:
  - provide a venue for research activity, giving all an opportunity to get involved in research;

- introduce a valuable skill to the residents, helping them to understand what goes into the development of a new drug or device.
4. Ultimately, clinical research helps both practitioners and residents to understand the technology and the associated treatments in new ways.

## Part 2: What does a research-oriented practice look like?

Conducting research is distinctly different from traditional practice. There are examination and monitoring protocols, forms, medications and/or devices which likely require very specific procedures for their use. As such, a research-based practice usually establishes separate staff and facilities as use for research-only. What follows are several of the considerations practitioners must take under advisement when deciding whether or not to establish a research-based practice:

### 1. Telephone Recruitment

- Initial contact with potential study subjects is usually made over the telephone. Potential study subjects usually are responding to an advertisement, are existing patients, or are referred by another physician.
- Both sides will usually have a long list of questions, so the person representing the practice must be intimately familiar with the study's details, as well as the inclusion and exclusion criteria. Because these criteria define the desired characteristics of the study population, detailed information about the potential subject must be obtained so that the study subject and the investigator's time is not wasted.
- The very nature of research demands confidentiality, so the practice will not be able to share much information about the study upfront. Practicing via role playing is a suitable method for preparing a practice's point person in how they should handle any unexpected questions or requests. Many times, difficult questions must be referred to the investigator.

### 2. Screening

- Blood work and/or basic processing of specimens, X-rays, gathering patient history and vital signs may all be part of the screening protocol, so a research-based practice must be set up to accomplish these tasks.
- If specialized tests are required, the sponsor usually will provide such training to the practice's staff.
- The screening process is often very specific, and thus very time consuming. A practice must account for an appropriate amount of time to do these tasks properly. Remember, study subjects inappropriately admitted to a study may result in injury to the study subject, and penalties and regulatory action against the investigator.
- In some cases, the screening process is spread out over several visits, so potential study subjects may have to return several times before they can be enrolled in the study.

### 3. Administering and Informed Consent

- The Informed Consent Form (ICF) is one of the most critical documents in the study process. All study subjects must sign the ICF before taking part in the study

- This document
  - informs the study subjects of their rights and responsibilities;
  - discusses the study treatment, alternatives, and incentives (if any).
- Study subjects are typically required to sign every page of the ICF, and must be given time to ask any questions with regard to the study protocol, risks, and alternative treatments. As such the person administering the ICF must be highly knowledgeable about the study protocol, and must answer any and all questions to the satisfaction of the potential study subject.

#### 4. Study Enrollment

- The study enrollment process begins once a suitable study subject is identified. Typically, this involves the Randomization Process.
  - Randomization is the act of placing a study subject into a specific treatment group, and determines which treatment the study subject will receive.
  - Once the randomization has occurred, then treatment is rendered.
- It is important to keep in mind that your office must have a secure place to store study drugs and materials. In some cases, refrigeration may be necessary (which may be supplied by the study sponsor). Temperature readings in the refrigerator may need to be taken on a daily basis.

#### 5. Evaluation

- Study subjects are evaluated on an ongoing basis, in accordance with the study requirements.
- This may involve any number of combinations of office visits, such as 3 follow-ups in a 2-week period, or 20 follow-ups over a period of a year or more. The study protocol will direct the investigator on what is necessary.
- The evaluation of study subjects is very specific, and may include the completion of forms, photographs, blood draws, or a host of other tests; office visits ranging from a few minutes to several hours; or interviews regarding any adverse events (also known as AE).
  - AEs include any problem the patient has experienced during the study period.
  - All AEs must be documented.
  - In the event of a serious adverse event (also known as SAE), the study sponsor and the Institutional Review Board, the organization that oversees the study subject's safety, will need to be notified immediately.
  - SAEs are typically serious or dangerous complications that occur, such as death of a study subject. They may or may not be related to the study.
  - AEs and SAEs sometimes are identified as a result of blood work done through the study, as opposed to patient interviews.

#### 6. Case Report Forms (CRF)

- All study data is recorded in Case Report Forms (also known as CRF). They are the official study documents by which the study outcomes are assessed. All data, adverse events, and any forms related to the treatment of a study subject are included.
- CRFs are completed using Source Documents, which may be an office medical chart or study documentation forms. Every item within the CRF should be verifiable from some data source.

- The study investigator is required to keep two sets of data: One set is usual medical records, and the other set is the data copied into the CRFs.
- CRFs are typically stored in notebooks, and must be kept in a location that is easily accessible when study subjects come in for their regular visits.

#### 7. Workspace for Study Personnel

- Because of the level of paperwork generated by clinical research, it is important to have easily accessible storage space for records, drugs, equipment – basically everything related to the study.
- Several monitoring visits will occur, so space must be available for monitors to work, as they review both the records and the work done by the investigator.
- Provide easy access to all records, including source documents (i.e. office records), and be sure that the investigator is available to respond to all queries the monitors may have. Scheduling an hour or two at the end of the work day is an appropriate strategy to follow.

### Part 3: Understanding the Structure of the Research System

Research protocols require governance, rules and regulations. To understand the structure of the clinical research system, it is important to understand the players involved and their roles in the research process.

#### 1. Food and Drug Administration (FDA)

- The FDA ultimately decides whether or not a pharmaceutical company has met the required burden of proof to establish that a particular drug is safe and effective. It also plays a role in determining what claims the manufacturer of a particular drug can make when marketing it to physicians or to the public.
- The FDA will verify that the data it is looking at is genuine by conducting audits of a percentage of the data collected. A representative of the FDA physically comes on-site and examines the CRFs and possibly the source documents. The audit may be pre-planned or unannounced, so it is critical that records are kept current.
- Based on their appraisal of the study and its data, the FDA may approve, require further data, reject, or even halt an unsafe study.
- Once the FDA is satisfied that a company has adequately proved its claims, a company may move forward toward its goal of releasing a product. Alternatively, it may request more data, agree that the research is valid and meaningful, or reject claims made about a product.
- The FDA also requires that all investigators are familiar with the rules of data collection called Good Clinical Practices (GCP).
  - GCP is the basis for the code of conduct that all clinical investigators must follow.
  - GCP violations can be very serious, and can result in investigators being fined or barred from research.
  - In order to insure that investigators are knowledgeable about GCP, a free certification course is available through the National Institutes of Health's web page, [www.nih.gov](http://www.nih.gov). Typically, it takes about one to two hours to complete.

- Research fraud is a very serious offense. Investigators who intentionally produce fraudulent data can be barred from conducting clinical research, fined or even receive jail time in the most serious cases.

## 2. Institutional Review Board (IRB)

- IRBs are organizations that protect the rights of those participating in clinical research studies. They are composed of physicians, scientists and members of the general public. The FDA requires IRB supervision before a clinical research study can begin.
- There are two types of IRBs:
  - Central IRBs. A central IRB may oversee many sites involved in the same study, so a protocol can be approved one time and be applied to many sites. Most studies involving doctors in private practice will utilize a central IRB. These are private and normally for-profit entities.
  - Institutional IRBs. Research sites located at hospitals and universities are usually required to use an institutional IRB. They have a responsibility to ensure the research meets both the standards of GCP and those of the institution as well. They may be involved in study design.
- The IRB review takes into account many issues:
  - Community attitude is considered when deciding on approval (cloning and genetic manipulation may be controversial in a given community, for example);
  - Informed consent forms are among the IRB's most important responsibilities. IRBs require
    - the form be written clearly, with minimal jargon;
    - a description of the potential risks, treatments and possible complications;
    - disclosure of the nature of the treatment, as well as describe alternatives if the subject does not wish to participate; and
    - a discussion of the consequences of premature withdrawal from the study, or if an adverse reaction to treatment occurs.
- The IRB is responsible for ongoing monitoring of the study. When it receives negative information about the study (adverse reactions, variations from study protocol), it is immediately evaluated. If deemed consequential, the information may be passed on to the FDA.
- The IRB may withdraw approval of a site if violations occur.
- IRBs exist principally to protect the rights of study participants and insure the safety of a study, not evaluate collected data.

## 3. Study Sponsor

- Usually a pharmaceutical company, or some business with an interest in the study.
- Sometimes, a study may be commissioned by one company to evaluate the performance of a competing company's product. In each case, the study sponsor is the person or company who pays for the study.
- In most cases, final word on all research matters, with regard to study design, implementation, assessment of data and release of data belongs to the study sponsor.

#### 4. Clinical Research Organization (CRO)

- CROs are usually hired by the study sponsor to implement a study. In some cases, the CRO may write the study as well.
- CROs allow study sponsors to conduct their clinical research at “arm’s length.” Introducing a third-party CRO can insulate the study from outside influence.
- They are usually large, multinational companies, familiar with the specific rules and regulations of different countries.
- CROs are responsible for hiring doctors and clinical sites for data collection.
- They monitor data collection, ensure that protocol is being implemented properly, handle study finances, and provide expertise to interpret study protocols.

#### 5. Site Management Organization (SMO)

- Large CROs often use SMOs to help identify sites to conduct research. They will recruit individual physicians, groups or sites which can provide study subjects for studies.
- In essence, the SMOs function as brokers, collecting a fee in exchange for the placement of studies with investigators. SMOs may provide some guidance to investigators as well (assisting with various forms and handling documents necessary for the IRB approval, for example).

#### 6. Study Monitors

- Study monitors usually are employees of the CRO and are responsible for traveling to the individual sites and reviewing all research records. This includes the case report forms, regulatory documents, drug logs and all aspects of data collection and research.

#### 7. Auditors

- Auditors typically work for the study sponsors. They review the work of the sites, and try to make sure that the monitors and CROs are conducting the research in line with protocol.
- As the voice of the study sponsor, they have the final word on all issues related to study protocol. Sometimes, audits are performed by the FDA as well.

#### 8. Investigators

- Investigators are the individuals responsible for collection of data. The Principal Investigator is the individual (usually a physician) who is ultimately responsible for every aspect of data collection related to the study.
- The Principal Investigator is specifically named on FDA Form 1572 in most studies. Other investigators at the same site are called “co-investigators” or “sub-investigators.”

#### 9. Study Coordinator

- Study Coordinators are employees of the site and aids the Investigators in the actual collection of research data, maintain study supplies, and keep the regulatory documents up to date.
- The coordinator may also keep drug and refrigerator logs, enrollment logs, and randomize study subjects.

- The study coordinator handles all of the daily issues, supporting the investigators to make sure that the study moves forward, within the guidelines of the study protocol. The Study Coordinator is absolutely essential for the success of most research programs.

#### Part 4: Critical Documents

All studies involve a large number of documents. These documents should be familiar to all clinical researchers, and include:

1. Curriculum vitae - This should include the address of the study site. A CV should be available for all investigators and all study personnel.
2. Form 1572 - Provided by the FDA, this form officially identifies the principal investigator and the study site. Any time there is a change in the location of the study site, or a change in the investigators, a new Form 1572 must be completed, placed in the regulatory documents notebook, and submitted to the IRB.
3. IRB Application - Most IRBs require the principal investigator to provide them with the details needed to examine a site for approval.
4. Informed Consent Form (ICF or IC) - The ICF is signed by the study participants. It describes their rights and responsibilities as a study participant.
  - There are several items that all ICFs should contain:
    - a description of the study protocol,
    - time commitments,
    - tests to be performed,
    - alternatives to the study treatments, and
    - remedies if a problem should arise.
  - ICFs must be presented in easily understood terms, free of technical jargon. Language must be approved by the governing IRB, and the ICF must indicate the name and contact information of the IRB.
  - Frequently, the ICF includes a section which guarantees the study subject's privacy. Unlike standard treatment non-treating study personnel will have access to patient medical records, and specific permission should be given for this. Coded ID numbers may be used to protect privacy.
5. Study Protocol - The study protocol describes the research project in detail. It includes inclusion and exclusion criteria, data collection protocols, and definitions of items critical to the study's methodology. Normally, there is an outline of each step of the study found here as well.
6. Contract
  - The agreement between the investigator (or the investigator's employer) and either the study sponsor or the clinical research organization responsible for the study.
  - Included with the contract is a budget and a full description of the responsibilities of each party.
  - It stipulates indemnification (each party relieves the other of responsibility provided the study protocol is followed). Most important is the fact that the study sponsor will not hold the investigator responsible if a problem occurs with the drug administered, provided it is administered according to the protocol.

## 7. Study Budget

- The study budget must be negotiated for each study. Sometimes, there is no room for negotiation, and a potential investigator must either accept or reject the offer.
- Assessing the reasonableness of the budget is an important. When considering the budget,
  - list all tasks to be accomplished, and assign a time value to each,
  - determine a reasonable hourly figure for investigators and for assistants or coordinators,
  - determine what tests, if any will be the financial responsibility of the investigator.
- Ethical and professional study sponsors will spell all of these things out in detail. Many investigators may also qualify for additional overhead funding in some cases, such as those affiliated with universities or large institutions.
- Make sure the terms of payment are crystal clear. For example,
  - Does the subject have to complete all study visits?
  - If the subject drops out before the end of the study, will payment be made for the time the investigator you spent up to that point?
  - Is payment made per visit, or per subject?
  - Is there any payment for screening failures (potential study subjects who you spend the time to evaluate, but ultimately do not qualify for the study)?

Either the budget or the contract should spell out when you will get paid.

- Do you get paid at the end of the study?
  - Is there start-up money available?
  - Do you get paid quarterly or when each subject completes the protocol?
  - In some cases, studies may not pay until the end, which means you may have to front all study costs for up to one year!
- All sites have costs that are specific to them, which may create differences between investigators/sites. For example,
    - in major cities, transportation and parking costs may be substantially higher than in rural areas,
    - experienced investigators may receive better funding than inexperienced investigators, since there is less risk that these investigators will deliver on the promise of study subjects.
  - Keep in mind that a budget that initially sounds very generous may ultimately require costly out-of-pocket expenses that make the undertaking not economically viable. Be sure due diligence is thoroughly completed.

## Part 5: Conducting a Study

Once a site and investigator have been approved to conduct a study, the hard work begins. Investigators must carefully follow all protocols and remain extremely diligent with their record-keeping. What can a new investigator expect? Though every study is different, most studies follow the same general pattern:

### 1. Types of Studies:

- Phase 1: First time in humans - these are usually the highest risk studies, and all study subjects are closely monitored.

- Phase 2: These studies focus on safety over a broad dosage range. These studies usually deal with some aspect of pharmacokinetics and efficacy.
- Phase 3: These studies focus on efficacy over a range of doses.
- Phase 4: These studies usually compare a new drug or device to existing standards. Submission of data to the FDA following the completion of a Phase 4 study may result in product being released for sale.
- Pivotal Study: A pivotal study is usually performed on drugs already approved by the FDA, where the manufacturer wants to make additional claims.

## 2. Investigator's Meeting

- The purpose of the investigator's meeting is to standardize the collection of data, review the quirks of data collection particular to this study, and review critical aspects of the protocol.
- Most study meetings include a review of Good Clinical Practices (GCP) expected of all study personnel.
- The Investigator's Meeting is usually attended by the principal investigator and the study coordinator. On the corporate side, there may be representatives from the sponsoring company, the author(s) of the study, study monitors, and scientists who played a role in the development of the drug or device

## 3. Recruitment – Getting study subjects in the door

- Finding study subjects often depends on the type of site or private practice you have.
- Patients can be referred from other doctors, drawn from your existing practice, or can be referred by other patients.
- You cannot pay for referrals. Kickbacks of any time are strictly prohibited.
- Since care provided through clinical trials is usually at no cost to the study subject, there is no concern about whether or not the study subject has insurance. Furthermore, many physicians may be eager to refer patients who are in need of advanced care, but cannot otherwise afford it.
- Perhaps the most common source of patients is through advertisements. All advertisements:
  - must be approved by the governing IRB, in order to insure that nothing deceptive is presented,
  - should clearly describe the type of patients sought, written in layman's terminology,
  - must describe any incentives, written in a manner which is not overly enticing.
- Target marketing is another popular technique. For example, for a study on diabetic foot ulcers, an advertisement in the local American Diabetes Association chapter newsletter would be productive.

## 4. Patient Screening- the critical step in bringing qualified patients into the study

- Telephone screenings are the first point of contact in many cases.

- The telephone screening should be performed by a person who is qualified to ask questions that deal with the inclusion and exclusion criteria. They must be very familiar with the protocol.
- They should discuss the study subject's time commitment necessary. If all factors seem to indicate that the potential study participant is qualified, they should be brought in for a personal interview. Once a qualified study subject comes to visit, the process of enrollment begins.

#### 5. Informed Consent – the beginning of enrollment

- Enrollment begins with the presentation and signing of the informed consent form.
- The study subject must be given adequate time to review the entire document, sign or initial each page, and be permitted to ask questions. They may also take a copy of the document with them.
- Subjects do not have the right to select the treatment they will receive in a randomized trial. They do have the right to withdraw at any time, however, if they are not happy with the outcome of the study.
- Once the informed consent has been signed, the collection of baseline data commences, and randomization to a study group usually occurs.

#### 6. Screening Visit

- Depending on the study, this may be the first visit between investigator and study subject. Any number of things may occur.
- For example, if the study deals with oral antifungals, an investigator may need to delay actual enrollment until liver enzyme levels are determined, and proof of a fungal infection is obtained through a culture.
- In other studies, screening and dispensing of the first treatment medication occur all on the same visit. Screening visits usually include the collection of baseline data such as basic labs, measurements, and photographs.
- As seems clear, getting a patient to the screening visit may require considerable effort on the investigator's part.
- Therefore, when an investigator develops a study budget, it is important to know whether or not any compensation will be forthcoming when a subject does not ultimately qualify for enrollment.

#### 7. Subject Enrollment and Follow-up

- Once a study subject has met ALL enrollment criteria, he or she is officially enrolled in the study.
- From this point on, the principal investigator and his or her associates must follow all study protocols and collect the necessary data.
- As noted earlier, follow-up required by the study may vary widely, from days or weeks, to months or years.

- Sometimes follow-up is dependent on clinical response as well. During follow-up, the study sites must monitor all subjects for complications or Adverse Events that may occur. All negative changes, whether or not they seem related, must be monitored and recorded.
  - In some cases, a serious complication may occur as a result of a study treatment or drug. This is called a Serious Adverse Event, or SAE. An example of an SAE would be that a study subject dies, or is hospitalized for a serious occurrence.
  - When an SAE occurs, the IRB must be contacted immediately. It is not uncommon for an IRB to completely halt a study following the report of an SAE.
  - All studies have some sort of endpoint defined. Either this is defined by the number of office visits, or some conclusion of treatment such as closure of a wound, etc. In some cases, for a variety of reasons, a study subject may withdraw from a study, and this also may be considered an endpoint.
8. Data Collection - Data collected during the course of a study is recorded in two locations:
- The official study data is recorded on Case Report Forms (CRFs). Data from the CRFs must also be recorded in the investigator's medical records;
  - The Source Notes are comprised of the CRF data, medical records, laboratory tests, and all other medical data. In the event of an audit, the auditor may ask to review the source documents to confirm that the CRF's were properly completed.
9. Study Close-Out – This occurs when the sponsor no longer wishes to collect data. There can be several reasons:
- The study has been halted,
  - All necessary data has been collected, or
  - There has been a safety issue leading to early termination of the study.

When a study is closed out, the study monitor will come on-site and review all data. The monitor will collect outstanding CRFs, retrieve unused drugs, and discuss long-term storage of records as required. He or she also will make sure the IRB is notified of site closure.

## Part 6: Conclusions

Research can be a great adjunct to, or even replace, a practitioner's private practice. It allows practitioners to become involved in cutting-edge medical care, and provides a highly professional avenue for promoting one's practice. However, clinical trials require time, effort and considerable attention to detail. There are no shortcuts in research.