CHAPTER 2

Scrounging Your First Study

> You cannot acquire experience by making experiments.
> You cannot create experience. You must undergo it.
>
> —ALBERT CAMUS

Landing your first study is somewhat akin to finding your first job. Remember the want ads, all of which said, "inexperienced need not apply"? Yet you can't get experience because you don't have experience. Just another Catch-22.

What Do You Need to Get Started?

Before you can apply to conduct studies, here's what you will need—at a minimum:

- An MD (or similar terminal degree) who will be the responsible party, or Principal Investigator (PI): The *Code of Federal Regulations* (21 CFR 312.60) makes it clear that "an investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation."[1]
- A study coordinator: This may either be an RN or your secretary, if this person is of the type formerly known as a jack-of-all-trades. In hiring such a person, remember the old adage, "Hire brains." In this case, it also helps if the person is pleasant, flexible, charming, compulsive, detail oriented, and extraordinarily well organized. Good study coordinators are rare jewels. Medical knowledge is a nice plus, but it is not at all essential as it

is more readily acquired than the rest of the desired qualities. Bank tellers or others who are detail oriented can become excellent coordinators.

- An institutional review board: This may be either local (at the individual study site) or centralized (a commercial IRB that provides services for multiple sites).
- A telephone.
- Internet access and e-mail capability.
- A fax machine (preferably with a time warp feature, as everything will have to be sent yesterday).
- Storage facilities for supplies: You might want to look for a former aircraft hangar, warehouse, or decommissioned nuclear power plant, given the volume of supplies and the need to store case report forms (CRFs) and other study records for eons. Extra locked facilities are mandatory if the investigational medications are being stored on site and for maintaining the confidentiality of patient records. If you are doing more than one study with electronic data capture (EDC), be aware that each sponsor will require the use of its own dedicated computer.
- A pharmacist, a phlebotomist, and lab, radiology, or other technical support personnel, depending on the protocol specifics.
- Money, money, money.

Your study site needs to be equipped with all of these before you can even try to conduct studies.

Starting in the research business is no different from starting any other business. You are likely to have significant start-up expenses and experience a cash flow crunch. Be aware that it will likely be months into a study before you see any useful amounts of money arrive from the sponsor or CRO.

Consider where you might borrow money. Options include credit unions, a local bank, microfinancing sources, and a winning lottery ticket. The Small Business Association (http://www.sba.gov) has a wealth of information on business plans and loans. In addition, business assistance programs are available for minority, woman, rural, and other special needs business owners.

View from the Trenches

This is how I got my first break.

After my fellowship in Morgantown, West Virginia, I moved to the middle of nowhere, the former Gateway to the West: Cumberland, Maryland. I had first encountered the town driving home from college some considerable number of years earlier, driving alone cross-country in a cheap "drive away" auto transport deal, when I had a tire blowout outside of town. It was an omen, a portentous sign to stop and settle here. After I struck out into solo practice, a mentor, the dean of the medical school where I had completed my fellowship, recommended me to his CRA, Ron Montgomery. The dean had been offered a study that he was too busy to do. Ron had to drive through Cumberland anyway to get to Morgantown, so he stopped, and over a period of months, checked out our site and me. Since we were on the route to points west, it was convenient for Ron to place the study here. It was also extremely low risk. It added no travel time for him, for example. From that initial break, the rest evolved.

With that first study, I established my reputation as a hard worker, generating good, solid data. The CRA and sponsor wanted to do repeat business, since developing our site was in their interest, and we were offered a wider range of trials.

I learned, on that study, that CRAs and medical monitors as a whole are an incredibly fickle and mobile group. They often move from company to company on a regular basis and are regularly reassigned within a company. You hope they will all take their little black books and their PDAs with them so that you can expand your horizons along with them.

What I hadn't counted on was that the first pharmaceutical company's monitors wanted to keep our site a secret from the competition. (They later described it as a veritable gold mine.) Unfortunately, they did too good a job. (Congress, or the White House, could learn a lot about avoiding leaks from these guys!)

Be sure to analyze your expenses, including employees' wages, taxes, and benefits; unemployment, workers' compensation, and liability insurance; and facility costs—rent and utilities, equipment, supplies, and shipping. Also, try to minimize your overhead. Start small and initially work with part-time or contract employees if you can so you are not locked into a crushing overhead.

Most importantly, perhaps, you need to have some insight into your strengths and weaknesses. Be willing to start out by focusing on your "specialty" and strengths; then broaden your business as you gain experience.

Navigating Site Selection: Landing Your First Study

You might consider several approaches for acquiring your first study.

Ask a Friend or Mentor

Word of mouth is your best friend, next to nepotism. Networking is extremely effective in coming by studies.

Rise Up the Food Chain: Overcoming the Catch-22

Being on the bottom of the medical staff food chain holds great risk: you might be taken advantage of either financially or in terms of receiving adequate credit for your contribution—in a sense, being devoured by the more senior staff. Traditionally, you could climb higher on the food chain in several ways. The most time-honored tradition of gaining the necessary experience is that of "medical training," a euphemism for indentured servitude. You work for slave wages under inhumane conditions to gain experience and, if you are lucky, to make some contacts.

The next link up is that of apprenticeship. I have trained colleagues in doing trials, largely out of friendship and collegiality, so they could see what they were getting into without having to make a large commitment. The hope was also that we would then help one another on future multisite trials and be able to provide backup coverage for each other. This arrangement has produced mixed results. A new investigator should consider proposing this kind of pact to a more senior physician in order to gain experience and access. The offer may well be accepted as extra help and, perhaps, regarded as an investment in the future, especially if the new person does not pose a significant financial threat (that is, if the new person is working in a different subspecialty or if the alpha male is nearing retirement). The downside of such an arrangement for the senior investigator is described by the old adage, "Give me a medical student who only triples my work, and I'll kiss his feet!"[2]

With luck and hard work, you can attain the status of subinvestigator. While these achievements may be small and incremental, they are useful for listing on your curriculum vitae and are a passport to greater opportunities.

One unfortunate change in the industry is that CRAs have lost much of their clout in placing studies. This change in strategy is not one of the smarter decisions made by the sponsors. CRAs know their territories well, have the leisure (relatively speaking) to check out potential new sites, and know their

investigators' abilities. They are excellent judges of where to place a trial. Now decisions are largely made in-house, by a centralized team distanced from the action and therefore unaware of site nuances or the unique personalities of sites and investigators. This is an unfortunate development for all.

Network

Informal networks are also quite an effective way to get studies. Ask colleagues at medical and investigator's meetings, for example, to ask their CRAs if any additional sites are needed for a current study. When you are later offered a different study, you can return the favor. Or you might be able to suggest far distant sites, with friends or colleagues that you have known for years. Reputation, networking, and the personal touch have, over the years, continued to prove the most constant and reliable source of studies.

Try CROs or SMOs

Some drug manufacturers not only design their studies but conduct them as well, having their own in-house management team and CRAs. Others farm the work out, subcontracting with other businesses to identify study sites, recruit patients, and perhaps manage the lab work or advertising while remaining as the general contractor on their (drug) building project. For example, the major subcontractors on clinical research trials are contract research organizations. These companies are agents for the sponsor, hired to find appropriate sites and to conduct the studies for the sponsor. CROs work for many different drug companies. (Site management organizations are similar but much less common. They work by marketing groups of sites to a drug company and by providing the management services to oversee a study for the sponsor.) The advantage of working with a CRO is that you are then entered into the organization's database, which is used for offering services to multiple drug companies. In the future, when the CRO needs a site for a specific type of study, it is likely to approach you again.

Newer Methods for Landing a Study

The techniques described above for attracting studies all evolved in simpler days. Other options for selling your site are now available and expedient, but they are neither as personal nor as gratifying. The primary route in vogue is registering with an on-line broker, as discussed below.

Medical sales representatives, or "drug reps," will be detailing you as a physician to sell their wares. Tell them that you have just completed a trial in a particular indication or that you are interested in a specific research area, and ask if they will suggest your site to their company's clinical development department. It's worth a try, but this is not a particularly effective route. (This method perhaps works better if the drug you recently tested was from one of their major corporate competitors.) In addition, investigators can occasionally attract studies by advertising, either in journals or by "hustling" at medical conference booths, but this approach also appears to be a less-effective route.

You should also do your own research, reading and studying industry forecasts for your area of interest. You can learn about ongoing and upcoming studies by exploring ClinicalTrials.gov and then contacting the pharmaceutical sponsor of interest. Conferences that are specialty or disease specific and abstracts of early research findings can provide important leads. Company Web sites and some commercial sites, such as those of CenterWatch, the Association of Clinical Research Professionals (ACRP), and the Drug Information Association (DIA) can give you important leads.

My favorite pharma news sources are Pharmalot's Ed Silverman (http://www.pharmalot.com), who can now also be found posting on the In Vivo

View from the Trenches

Life in the Wilderness

Although living in the relative wilds of western Maryland has its charms—such as the bear visiting me in my garden paradise while I was writing this book—it can feel rather isolated at times. Fortunately, with the Internet, you can research most topics from anywhere. My favorite pharma news sources on my Google Reader feed are Pharmalot's Ed Silverman (http://www.pharmalot.com), Mark Senak's Eye on FDA (http://www.eyeonfda.com), and Wired's Med-Tech (http://feeds.wired.com/wired/medtech). It's also really easy to set up Google News Alerts for almost any topic you might imagine—including investigational trials for whatever condition might interest you.

Other handy sites include Clinpage (http://www.clinpage.com), FDA News (http://www.fdanews.com), DIA Daily (http://www.dia.custombriefings.com), FiercePharma (http://www.fiercepharma.com), Contract Pharma (http://www.contractpharma.com), and Outsourcing Pharma (http://www.outsourcing-pharma.com).

Blog (http://invivoblog.blogspot.com), Mark Senak's Eye on FDA (http://www.eyeonfda.com/), and Wired's Med-Tech (http://feeds.wired.com/wired/medtech). It's also really easy to set up Google News Alerts for almost any topic you might imagine—including investigational trials for whatever condition might interest you.

Register with an On-Line Site-Listing Service

Increasingly, investigators with study sites to offer have successfully turned to on-line site-listing services, such as CenterWatch, Research Investigator's Source, Inclinix, or Site Management Solutions, where they can list their experience and areas of research interest. This information becomes part of a database, which can then be searched by the drug company sponsoring an upcoming trial. The use of a database is somewhat limiting, however, as the format does not allow for any description of unique attributes or qualifications of the site. But this format may still be useful for attracting initial attention to a well-trained investigator with little experience. (I particularly liked the now-defunct Clinmark, because I could readily see who had accessed my listing.) The downside of registering with a commercial database is that the listers are often required to pay several hundred dollars. While this cost can be recouped, it is expensive for the beginning investigator and seems akin to a dowry offering.

Register with an On-Line Broker

You might also consider listing your research site with a study broker, especially if you are new to trials. A study broker is a middleman who connects sites and sponsors—for a fee. Unfortunately—and to my mind, unfairly—the fee comes from the investigator rather than the more well-to-do sponsor or CRO. Part of the broker's business is keeping up with the constant personnel changes in the industry; part is monitoring drug development and becoming aware of new opportunities. Investigators can do this themselves, at less expense, through their own industry research or through subscription services such as TrialWatch, but it is considerably more time-consuming than relying on a broker.

So the broker plays matchmaker, introducing the sponsor and investigator. If those two parties agree, the investigative site pays the broker a fee, typically 10 to 20 percent of the grant. If all parties are happy, they will repeat the process in the future.

Unlike a site management organization, a broker is generally not involved with the logistics of the pretrial activities—the budget and contract negotiations and the regulatory hoops. The site and sponsor handle these details directly. But the broker might, on occasion, serve as a sort of marriage counselor, helping the two sides work out differences in expectations.

A significant advantage of using a broker is having the opportunity to learn about more studies so you can fill unexpected gaps in your workflow. In theory, if all goes well with the arranged trial, you may have future opportunities to contract directly with the sponsor, without the middleman. However, lapses in institutional memory mean that the sponsor may not remember your good work and, in the worst case, you would have to work through a broker again. But, as Joe Bollert, president of Investigator Location Services, notes, "90% of something is better than 100% of nothing."[3]

Be a Coauthor

Being listed on a publication is an elusive but useful goal and something worth negotiating for in a contract. For example, if you are listed in the fine print on a publication about a pneumonia trial, another sponsor might follow this lead and call you, looking to place a different pneumonia trial. Most sponsors will not agree to list you on a publication as coauthor, but some will, stipulating that coauthorship will be based on enrollment. Only the top two to three PIs will win this valuable prize; this is another incentive for the PI to work hard on the study. Get it in writing! Don't rely on an oral commitment. In one case, although one investigator was far and away the leading enroller, that investigator was not part of the sponsor's long-term strategy or marketing plan, which relied on name recognition of investigators on publications and presentations. Therefore, the sponsor did not want the investigator to be the coauthor and did not list that person on the study. This disillusioning experience was one of the investigator's more embittering lessons. Remember—get everything in writing.

When a New Drug Application receives approval, the list of investigators working on the protocol becomes public information that is then occasionally mined by other drug companies. But it takes years after a trial has begun before the NDA is approved—if it ever is approved—so you shouldn't count on this route to recognition.

Why It's So Difficult to Get Studies

Several factors contribute to the difficulty some investigators may have attracting studies even when they have been previously successful. Twenty years ago, site-sponsor relationships seemed more friendly and cooperative. Since then, as pharmaceutical companies have swallowed each other up, many internal processes have become centralized in an organizational attempt to become more lean and mean. As the companies became more enamored of the bottom line, they further consolidated. This centralization results in the sponsors becoming increasingly distanced from the study sites, and the personal touch has become less important. As Ron Montgomery, an experienced former CRA and consultant, aptly observes, "Developing long-term relationships has become secondary to getting the job done for the least amount of money and grief. They talk about developing relationships but in fact do the hard line, confrontational, 'business-like' thing more often. Time is money, and 'what have you done for me today?' applies."[4]

Also, there is now a more rapid turnover of company personnel and less loyalty to and from a company. This turnover of staff contributes to the lack of "institutional memory" that may plague the attempts of an investigator to attract further studies. This holds true even when an investigator has performed well, if the product has not. In that case, the product may be abandoned and the sponsor's team scattered to work on other drugs in development. The sponsor's team may not associate your site with the ability to study other indications successfully. Surprisingly, many pharmaceutical companies reportedly do not maintain their own databases regarding their investigative sites.[5]

KEY POINT
Having a large patient pool and rapid turnaround time for IRB and administrative details will win you studies.

Unfortunately, sponsors and CROs are also increasingly using databases to weed out sites, not just to identify potential fertile new ground. Sponsors are increasingly removing the human element and instead relying on healthcare data to determine site selection and help with patient recruitment.

Data Mining

Using electronic healthcare claims data, one company claims to have "de-identified medical and prescription claims records for over 220 million U.S. patients. This longitudinal data, dating back to 1991, is comprehensive,

precise, and updated in real time as healthcare claims are submitted nationwide from 355,000 physicians, 1,500 hospitals, and over 25,000 pharmacies." So 220 million patients are linked "to their individual diseases and drug histories over the past 10 years" and these data are available to sponsors and CROs to identify potential sites and patients for specific studies.[6] For example, in oncology consortiums using electronic medical records, patients with a specific stage of a specific tumor can be readily identified, along with details about their geographic location, attending physician, and prior healthcare utilization.[7]

The level of commercially available detail about potential patients is astonishing to me. Most surprisingly, the company mentioned above claims that "methodologies and data sources are fully compliant with the federal regulations of the Health Insurance Portability and Accountability Act."[8] Yet ironically, individual sites and small centers are unable to successfully identify potential subjects because of the stranglehold HIPAA has at the local level.

Opportunities Do Exist

Rather than using experienced CRAs in the field, site selection is increasingly conducted by a rigid set of yes/no criteria with little allowance for uniqueness. Also, experience and enthusiasm are not the high priorities they once were. Rapid turnaround time and a large population base seem paramount. Name recognition also ranks higher than many other attributes. Switching from a personal assessment to rigid binary computer-based screening seems shortsighted, but it correlates with the increasingly frenetic pace at which sponsors want everything to be done.

Despite this shift in how companies place studies, an interested physician can attract studies successfully. As noted in chapter 7, there is an increasing need for Principal Investigators. In 1995, almost 12,000 doctors were listed as PIs for the first time on Form FDA 1572, the "Statement of Investigator," by which they agree to abide by the federal regulations for use of investigational drugs.[9] This number rose to 26,000 investigators globally in 2007, but only about 14,000 of them were in the United States.[10] While the absolute number of investigators has not decreased, the number of new investigators is not keeping up with the pace of new trials (1.7 trials per investigator in 1985 versus 3.3 in 2005).[11] More and more of these physicians are office-based rather than academic. Furthermore, 52 percent of investigators conduct only one clinical trial; only 14 percent conducted more than four trials between

1988 and 1997, suggesting that success begets further success.[12] Some investigators have nearly given up their regular patient practice and are focusing almost entirely on conducting clinical trials. This business-oriented approach has shifted the norm of conducting 2 to 4 trials at a site at a given time to conducting 13 to 14 at a relatively new type of site: a "study mill."[13] The turnover among investigators is rather high, so good opportunities are available for entering the field of clinical trials. Being experienced in the indication and having performed well for a sponsor are likely to get you further studies.

Site Selection: Be Careful What You Wish for—You Might Get It

In a recent article, Hassan Movahhed, then senior clinical director at Amgen, noted that "one-third of the doctors who sign up for its trials each year never return, a huge loss in institutional knowledge and money."[14] This is quite intriguing. Others note that 54 percent of new investigators are never used again.[15] Given this finding, it's even more surprising that the drug companies haven't been more creative and innovative in identifying study sites. One would think that sponsors would turn to doctors and sites that not only enjoy doing studies but also do them responsibly and competently. The drug companies should cultivate that type of site to run a variety of

View from the Trenches

In a sense, my specialty becomes almost irrelevant to my ability to conduct many types of trials. I like being the Principal Investigator on trials, especially working on new types of therapy. *I know how to conduct trials well at my site.* I have the capability of networking with other doctors in other specialties and gaining access to their patients and their knowledge of their specialty. Much of the specific pathophysiology, or medicine, I can learn (and demonstrate competence in, if need be), just as I have to learn new things every day as part of my regular patient care practice. The ability to conduct clinical studies should be regarded as a specialty of sorts, in and of itself.

I saw an interesting model of this some years ago at a study site I visited to better learn the ropes. In this particular case, an RN study coordinator ran the site within a large multispecialty practice. She conducted all aspects of the trials except for the medical assessments that required a physician, whom she hired as a subcontractor and trained.

studies. This would be far more efficient for both the sponsor and the site personnel. Learning each other's quirks and idiosyncrasies eliminates a lot of inefficiency and waste. However, the FDA would also have to be willing to try this model, since one of the current triggers for an FDA audit is, in fact, a PI conducting a trial outside of his or her area of expertise.

The extraordinarily wasteful and rapid turnover of sites appears to be caused by several factors at work. Some site teams may not be able to complete a project as readily as they envision. A rule of thumb is that one-third of centers (sites) will recruit no patients, one-third will recruit 20 percent of all patients enrolled in a study, and one-third will account for 80 percent of the enrollment.[16] A more recent Harvard Business School study confirmed this adage, noting that 30 percent of sites failed to make a significant contribution to subject recruitment, and 70 percent of PIs perform only one trial with a sponsor.[17] Often, the key opinion leaders (famous doctors in a field who can mold opinion) do not contribute any significant portion of the enrollment—they provide the experience and prestige instead of the patients.

Another factor is money. The opening and closing of nonproductive sites now costs more than $30,000. This amount includes personnel costs and travel to the site for qualification, training, and initiation visits. Delays in enrollment or completion of a study result in an additional $40,000 per day in direct sponsor costs.[18] Sponsors are thus not likely to reinvest in a poorly performing site. On the other hand, even if you have worked with the sponsors or CROs before, they are likely to duplicate site visits because little communication exists between the different teams of monitors. (We recently had two qualification visits from the same CRO during one week, despite my suggestion that they combine forces!)

Some investigators probably have misjudged the amount of work and aggravation involved, the initial capital needed, the amount of lag time before they receive payment, and the cost of conducting trials. Dr. Harold Glass, founder of DataEdge and professor of pharmaceutical business at the University of the Sciences in Philadelphia, has analyzed this problem further. He concludes that a site must have about four or five studies running to be profitable, both in financial terms and in terms of the effort required to build a solid infrastructure.[19] Experience has shown that a small practice can do well with only two to three studies running at one time, depending on the type of protocol.

Site Selection: Why a Site Is Chosen, or a Marriage of Convenience

Once a sponsor has shown a nibble of interest, other attributes are factored into the question of placing a study at a particular site. One is the geographic convenience of the site for the sponsor or CRA. It is expensive for the sponsor to place a study in an obscure place. A convenient location is a good selling point and would undoubtedly help in your initial success. (Being charming, as well as exuding competence when a sponsor's CRA visits your site, can then clinch the deal.)

Being able to make a convenient driving loop of small sites made placing studies at my site attractive to several CRAs and sponsors, as it met their needs for efficiency and reduced wear and tear on the monitor (CRA).

Being available for the site qualification visit is crucial in landing a study as well as in establishing your image and reputation. Be prepared. Read the protocol and make notes on things you don't understand. Ask about inclusion and exclusion criteria that appear to be problems based either on your previous experience with studies or on your knowledge of your patient population. Have the protocol and your list of questions ready. Do your homework. Show your interest, and ask questions! A surprising number of CRAs and medical monitors express amazement that an investigator has

View from the Trenches

I have always regarded CRAs as my guests and tried, from the initial phone contact, to make them comfortable and meet their needs with a personal touch. I know they are tired of traveling and of being in cookie-cutter motel rooms in towns that may appear interchangeable. Make your site a pleasant interlude for them. I advise them about the best route from wherever they are coming from and direct them to scenic locations, pit stops, and good places to rest and eat en route. I try to match their interests and budgets with distinctive places to stay here in town. Occasionally, CRAs will mention hobbies or personal interests, which I will then try to follow up on as their host and tour guide. Our town is quiet, to put it mildly. A traffic jam is three cars ahead of you at the stoplight. But that slow pace and the beautiful scenery is a welcome break for many CRAs who are otherwise quite stressed from their frenzied, pressured job and urban travel adventures.

It never ceases to amaze me when CRAs express astonishment that a PI will meet with them at all, let alone try to be friendly and helpful. It just comes down to regarding them as people, with unique personalities and needs, and trying to be a hospitable host. I guess my mom instilled that in me.

actually read the protocol and paid attention to some of the finer details. How could it be otherwise? A deliberative approach is not only the rational way to approach protocols but shows a business suitor that although you may be inexperienced, you are thinking, credible, and compulsive.

If your mind is engaged, you can always learn. Curiosity is the first step; attentiveness is the second. If you have no interest in the protocol, you will transmit your attitude to the CRA, who will then not bother to place the study with you. An old adage, shared with me as I set out from training into the real world, advises that the keys to success as a consultant are "availability, affability, and ability," unfortunately, in that order. The same is true in relationships between a site and a sponsor.

Site Qualification Survey—Recording Your Experience

Before committing considerable time and resources to your site, the sponsor or CRO will do an initial assessment of your capabilities by sending you a site qualification survey. The sponsor doesn't always require previous research experience. It wants to know whether you have the types of patients the study requires and if you have a large enough patient pool.

After your first study, to make acquiring subsequent studies easier, it is extraordinarily useful to develop your own outcome data. Tracking your own experience helps demonstrate your credibility as a serious researcher. It also helps you assess study feasibility and budgeting for future protocols.

One reliable way to sell a study site is to develop a research experience summary or site profile. Make your profile look professional, and highlight the unique strengths of your site, be they special facilities, background, training, or certifications. Emphasize your experience, especially if you exceeded any goals. Some suggest developing a marketing package including a one-page cover letter with your logo, the name of the person you have in common with the recipient (or who is introducing you), references, standardized curriculum vitae for your site's personnel, and your outcome data.[20] Your research experience summary or site profile should include the following items:

- Indication (e.g., sepsis, community acquired pneumonia [CAP], or intra-abdominal infection) and type of drug (e.g., monoclonal antibody or antibiotic).

- Screening-to-enrollment ratio, or the number of patients screened for acceptance in the study compared to the number of patients who are then enrolled in the study.
- Number of patients agreed to in the study contract.
- Number of patients actually enrolled per unit time (e.g., one to two patients enrolled per month).
- Evaluability, or the percentage of patients who meet all the inclusion and exclusion criteria and complete all the protocol requirements. If the patients are nonevaluable, they won't be able to support the study drug's claims. If your site has a high percentage of evaluable patients, even if only a small number of patients, then it is a valuable and cost-effective site for the sponsor. If you enroll many patients who are not evaluable, the data are not useful and your site may be viewed as inefficient and unnecessarily costly.

This summary will also be quite helpful to you in answering the next sponsor's site qualification (also called site feasibility) survey. This survey doesn't always require previous research experience. The sponsor wants to know whether you have the types of patients the study requires and if you have a large enough patient pool. It is important that you try to answer the survey accurately. While this form can be a nuisance to complete, doing so will likely gain you entrée to the next stage, the first site visit. (For a sample "Research Experience Summary" and a sample "Site Qualification Survey," visit http://conductingclinicalresearch.com.)

Site Qualification Visit, or "Shall We Dance?"

The site qualification visit is somewhat akin to meeting a blind date. At the beginning, it is a ritual courtship. Monitors will be checking you out. They will review the protocol to assess your interest, level of understanding, and capability, as well as the overall experience of your team. Similarly, they will assess and review your understanding of regulatory requirements and good clinical practices (GCPs). The monitors will also view the general neatness and ambience of your office as a microcosm representing other aspects of your practice.

Monitors will check whether you have adequate staff to conduct the study and whether you are running competing studies. They will tour the site to evaluate your facilities, such as the lab, radiology, and pharmacy. In particular, they will focus on the security and storage conditions for the investigational med, as well as the pharmacy's capability for managing drug accountability. Often, they will want to meet other members of the study team, such as the lab manager, microbiologist, and study pharmacist, again to assess their level of commitment, enthusiasm, and experience.

The CRA will also be quite interested in seeing what, if any, space you have for him or her during a monitoring visit. It needn't be fancy, but comfortable surroundings are definitely a plus. Monitors, too, like creature comforts—a small but clearly designated workspace, such as a study or dictation carrel, and access to a photocopier, a fax machine, a telephone, coffee, and a bathroom. Many monitors claim to be oblivious to light, so a small niche in the dark recesses of the medical records department or a converted closet will do if need be. On the other hand, an attractive setting (such as our rural site with views of beautiful mountains and almost no traffic or crime) can be an added enticement that may serve to mitigate other inconveniences.

Monitors will assess what kind of patient population you have and whether patients are likely to be compliant. They will ask from where you draw your patient base, how many patients you have with the health problem of interest, and how you have derived your estimates. You might have gathered this information from a computer search of your own or the hospital's medical records, or from data showing your previous enrollment on a protocol for a similar indication. The monitor will review protocol requirements and assess recruitment strategies for your target population, again with an emphasis on compliance with GCP. Protocol requirements will be detailed.

The CRA will request a CV, the equivalent of a pedigree, and licenses for all involved. He or she will also review required regulatory documentation, such as Form FDA 1572. (For a sample "Site Qualification Visit Agenda," visit http://conductingclinicalresearch.com.)

Try to get to know the visitor to sense whether you are an appropriate match so that there will be less chance of "morning-after" regrets for either party. You might guide the CRA or suitor around your hospital personally, rather than delegating the tour to your staff. The time invested here presents a good opportunity for assessing the CRA and the sponsor company's

projected persona, as well as serving as an opportunity for bonding and for selling your site.

What the CRA or Sponsor Will Be Looking for at Your Site

To help you prepare for your initial site visit, here is a list of the types of information the CRA or sponsor will be looking for:

- Evidence that the right patient population exists.
- Pedigree of the investigator and staff (aka credentials).
- IRB turnaround time or the ability to use a central IRB.
- Turnaround time for grants and contract negotiation.
- From where (and how) patients are likely to come: sources may include the investigator's practice, other referrals, advertising, or other sources.
- Ongoing conflicting or competing studies.
- Experience level of the PI and the coordinator.
- Attitude: You need to convince the CRA that you really are enthusiastic and committed to doing the study. Otherwise, why should the sponsor bother with your site, since you are unlikely to meet your commitment toward the enrollment goal? Remember, it costs the pharmaceutical company a great deal of money to set up and monitor a site.
- Willingness to follow GCP guidelines and the sponsor's SOPs (standard operating procedures).
- Contracts and facility letter requirements: who must approve this study?
- Office organization.
- Facilities (e.g., lab and x-ray facilities).
- Ability to use a central reference lab and handle "send-outs," or specimens that need to be shipped to a central reference laboratory, and whether your facility will allow this. Occasionally, hospitals might insist that specimens also be run in duplicate (i.e., one run at the hospital as well as a second sample sent to the reference lab).
- General atmosphere.

- Creature comforts for the CRA: Is there a workspace available? Access to medical records? Necessary equipment and accommodations?

The adage that the keys to success as a physician are availability, affability, and, lastly, ability has been modified for investigators as follows:

> ***Recipe for Site Qualification Visit Success***
>
> *2 cups availability*
>
> *2 cups affability*
>
> *1 cup ability*
>
> *3 cups enthusiasm*
>
> *2 cups obsessive-compulsiveness and attentiveness to detail*
>
> *Flavor with appropriate amounts of essence of organization, ambience, and other auras, as desired. Top with a large dose of being genuinely nice and a personal touch.*

We've focused a lot on how you can prepare for qualification visits and try to attract studies to your site. You should also ask yourself how comfortable you will be working with the sponsor and the CRO or sponsor staff that you have met. Consider what information you might still need to decide whether you want to work with them. Are they a good fit stylistically, or have warning signs been raised by their attitude or manners? Do they appear to be responsible and ethical in their approach to the study question and design? And, most importantly, do you want to work on this problem, and with these people, for the next year or more?

Do Size and Setting Matter?

A decade ago, most clinical trials were conducted at universities. By 2000, the academic centers' share had declined from 75 percent to less than 40 percent.[21] From 1994 to 2009, the market share of independent, community-based research sites increased from 37 percent to 76 percent.[22] While many would decry the shift from academic to clinical practice settings, this concern is largely unwarranted. The shift reflects the reality of patient care and presents a more real-world view of future experience with the drug under study.[23] Many university patients are indigent, with multiple medical problems that have often been neglected for years. This population tends to have more problems

with compliance and loss to follow-up, that is, patients fail to return and cannot be reached by telephone or mail. Some of this is related to lower levels of education among these patients and some to inadequate social support. Certainly, huge cultural barriers have reduced trust and compliance in many settings, particularly in cities. Patients drawn from your practice or referred by colleagues are more likely to be compliant and to complete a study than are patients with whom you have no underlying stable relationship. I strongly believe that the type of patient seen in many community practices provides a more accurate portrayal of future drug use and experience than do inner city populations.

Community clinicians are often disparaged by academicians as "LMDs" (local medical doctors). But the quality of trial data is in large part determined by the quality of the protocol and is independent of the site where the patients are accrued. Prominent academicians are often too far removed from actual patient care. Keep in mind, too, that for most phase 3 protocols, a typical rate of expected patient accrual might be one or two patients per month. It makes sense for the sponsors to maintain wide networks of sites, similar to the way idle computer power is harnessed through decentralized Internet webs. So the two types of settings—academic centers and community-based practices—may well serve to complement each other.

KEY POINT

The main ingredients for scrounging a study are the leading characters at the site, the PI and the coordinator. Remember—a good coordinator is a rare find. Treasure him or her.

Enthusiastically promoting your site, especially if you are new or rural, is critical to landing a study. When selling a small site in competition with a name brand university, you can outline the advantages of being small and rural as follows:

- Community and private practice advantages:
  - Probably greater accessibility and convenience for patients, factors that encourage treatment compliance, study retention, and follow-up.
  - Small-town, down-home, personal atmosphere.
  - Personal treatment, attention, and even pampering for both the study participants and the visiting CRAs.
  - Consistency of evaluations due to fewer people making assessments.
  - Compliant patients, known to the individual investigator and rarely lost to follow-up. This is a significant advantage and should be emphasized.

View from the Trenches

I offer an unparalleled consistency because, with rare exceptions, I do all the study visits myself. (These are visits required by the protocol, where specific protocol-related examinations and testing are done.) The house staff does not change from day to day; one individual can more readily notice and assess subtle changes in patients.

If investigators draw patients from their own practices, they can be good judges of the patients' likely compliance and retention in the study. Also, investigators are trusted and respected by their patients and can thus further influence patients' compliance.

- Think of your own site's advantages or unique attributes and add them to this list.

- Major university's advantages:
  - Name recognition.
  - Aura of academia.
  - Larger pool of available subjects.
  - Generally more convenient and readily accessible for monitoring.
- Community and private practice site disadvantages:
  - Lack of panache.
  - Smaller pool of available volunteers.
  - Possibly greater inconvenience and expense for the sponsor to conduct site visits.
- Major university's disadvantages:
  - Cumbersome bureaucratic administration.
  - Poor maneuverability and responsiveness. The university may have a slower response to change due to its larger size and numerous layers of people to deal with (e.g., a large, lumbering elephant versus a speedy, agile mouse).
  - Slow IRB and legal reviews.
  - High fixed costs.
  - Attitude of entitlement.
  - Disdain for clinical research as opposed to pure bench work in "real," or basic, science.

- Cost of conducting a clinical trial approximately 10 percent higher than at unaffiliated sites.[24]

Private study sites have greater flexibility and maneuverability because fewer people and fewer administrative levels are involved. Interest and enthusiasm about the study is higher: "We're doing the study because we want to, not in obedience to a decree from above." Overhead is lower, a major advantage. Start-up time is shorter because fewer people and fewer levels of bureaucracy generally mean more rapid approval of contracts, protocols, and similar details.

So a persuasive argument can be made to the CROs or sponsors for placing studies in smaller, more rural settings. While this decision might add some initial inconvenience, the sponsors may well get a better return on their investment in rural sites than they would in sites in the bigger cities.[25] Trial organizers can draw from a larger and potentially more diverse group of patients if they are placed over a broader network of communities.

Conclusion

In summary, word of mouth and networking are the most reliable, successful, and pleasant routes for landing your first study. When you have acquired your first study, establish your reputation for providing quality work. The old-fashioned, simple ways of hard work and excellence are still the best.