CHAPTER SIXTEEN

Recruitment, Retention and Compliance

This chapter covers three of the most difficult aspects of conducting clinical trials: recruitment of subjects into the trial, retention of subjects after they have been entered and subject compliance with the protocol throughout the study.

Recruitment of Study Subjects

Finding, enrolling and retaining study subjects are some of the largest and costliest challenges facing clinical research professionals today. Enrollment may undoubtedly continue to be problematic in the future. Around the world, more than 80,000 study sites a year are involved in carrying out research based on 5,000 to 6,000 unique protocols. More than one million volunteer subjects will complete these trials.[1]

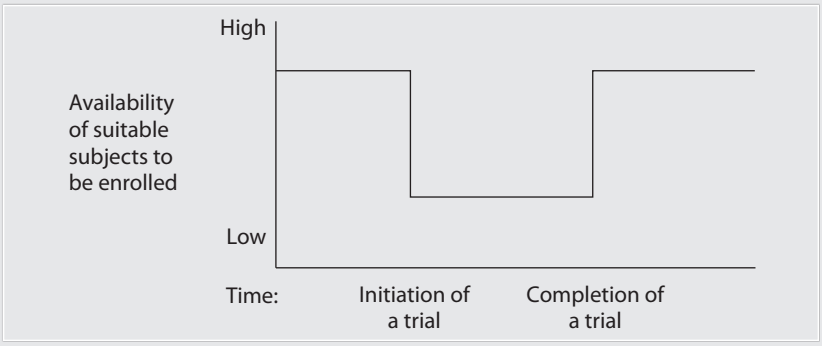
In 2015, more than $140 billion is spent on global R&D activity and the average cost to develop a successful drug is $2.6 billion.[2] The average cost of developing one new drug has increased to over $1.24 billion, and the development process time from the preclinical stage to FDA approval averages about seven years.[3] Given the enormous development costs, it is obvious that companies want to speed up the process as much as possible, allowing for more marketing time before their patent protection for the product expires. The timely enrollment of appropriate subjects into trials is critical to managing the timelines for a development program.

Lasagna's Law

Knowing the patient population and being able to accurately estimate the number of subjects that can be enrolled are critical to completing a trial within the given time period. Before a study actually starts at an investigative site, there always seem to be more than enough potential subjects waiting in the wings. For some reason, however, it frequently happens that as soon as the

trial begins, these potential subjects disappear. This is known as Lasagna's Law,[4] and can be shown visually in Figure 1:

Figure 1: Lasagna's Law



Lasagna's Law is like a corollary to one of Murphy's laws, namely, "whatever can go wrong, will." In the case of Lasagna's Law, when the study is over, there seems, again, to be plenty of suitable subjects.

Estimating Enrollment Potential at Sites

One of the most important pre-study activities for a CRA is to help sites accurately estimate the number of subjects they can reasonably expect to enroll in each trial. Investigators frequently overestimate the number of potential subjects they have, often because they are looking only at the number of potential subjects who match the overall diagnosis, for example, depression. However, there are a number of other factors that must be weighed and taken into account, including the protocol inclusion criteria and the subjects themselves.

Protocol considerations include the inclusion and exclusion criteria, activities and logistics. The largest constraints on enrollment usually are the inclusion and exclusion criteria for study entry. These criteria delineate the specific characteristics of the population to be enrolled. They will include demographic parameters, such as age, sex, disease and diagnostic criteria, and study-specific requirements. In a study of depression, for example, the following (simplified) inclusion/exclusion criteria might be found:

- Age 18 to 65 years.
- Men and women who are post-menopausal, surgically sterile or using acceptable birth control.
- Depression lasting at least six months, but no longer than one year.
- No previous depressive episodes before current episode.
- No previous treatment with anti-depressive medications.

- Not taking any other medications that might interfere with the study medication (list provided).
- Able to read and comprehend the informed consent document.
- Willing to sign the informed consent.
- Able to swallow pills.
- Able to make weekly visits to the clinic site for three months.

Let's look at how these criteria might affect the ability of a site to enroll subjects.

The upper age limit of 65 may restrict enrollment from sites that treat a large geriatric population. Depression is a disease that tends to recur in people over time, so the criterion that disallows previous depressive episodes would be a problem. The criterion disallowing previous treatment with antidepressants will be a big factor, because if these subjects are already in the care of the investigator many of them already will be on anti-depressive therapies. Willingness and ability to make weekly clinic visits are apt to interfere with a potential subject's life situation, especially when working. On top of these problems, many people just are not willing to participate in research, especially if the protocol requirements are burdensome and they do not see much potential value to themselves for participation.

How can these factors influence the ability to enroll? If a CRA takes the number of subjects a physician has in his or her practice who meet the diagnosis for the study (depression), then halves that number for each major inclusion/exclusion criteria, the number that remains is apt to be close to the number of subjects who will be enrolled. If we assume in our example that the site does not see many geriatric patients, then the four main criteria we need to be concerned with are: no previous episode, no previous treatment, no current medications for depression and willingness to sign a consent form. Let us also assume that the investigator says there are about 400 patients in the practice that suffer from depression. Take 400 and divide it in half for each of four major inclusion/exclusion criteria.

$$400 \rightarrow 200 \rightarrow 100 \rightarrow 50 \rightarrow 25$$

The CRA can assume the site probably will be able to enroll about 25 subjects into the study, in total. This number may be acceptable, but the rate of enrollment needs to be factored in as well. [Note that if a site regularly does research similar to the protocol in question, it may be able to estimate enrollment much more accurately based on its recent experience. In this case, there should be hard data about recent trials, including the inclusion and exclusion criteria, numbers of subjects enrolled and rates of enrollment to back up the estimate.]

The CRA must help the investigator analyze the requirements for the rate of enrollment. The sponsor may expect, for example, two patients to be enrolled every week, for the total of 25. Two patients a week does not seem too onerous, but remember that we have a three-month study, and that subjects