INTRODUCTION
In 1923 a reporter asked George Mallory why he wanted to climb Mt. Everest. The famous reply “Because it's there”—whether actually Mallory's words or the reporter's—came to epitomize this characteristic of doing things for their own sake—and, in Mallory’s case, of dying for them.

At one time or another most of us do things “because they're there,” although Herculean mountain climbing, like good steak, tends to be rare. Success in these sorts of endeavors gives us satisfaction, proves some point or other, and begets admiration. As for practical use, that is not really the point.

Those doing basic science will tell you they seek to solve problems for their own sake. Much of their work goes unnoticed except perhaps by a handful of experts in some subspecialty or other. Yet, every so often their ideas do reach industry where necessity is the most common ancestor of invention. And because need is the fundamental driver of industry, it will unashamedly ask, “What is it good for?”
Now as far as questions go, this is a pretty good one. The answer will mark your target and, in our own particular language, define your product’s intended use. It is certainly useful to mark your target if you hope to get there. It is also worthwhile repeating the “What is it good for?” question throughout the development process and even after. This is because targets can change, and, like children in math class, multiply. Aspirin, for example, was developed to treat pain and fever and is now also used for preventing heart attacks. Similarly, a drug for the treatment of colorectal cancer has been shown to be effective in treating a degenerative eye disease. And then there are drugs like Viagra.

So the question “What is it good for?” is basic, and it may be the most basic of all. At the same time it is often too general to be of practical use when planning a specific clinical trial. For example, suppose you have developed a device that is implanted in the body for monitoring blood flow from the heart to the lungs. This is important information for physicians treating patients with congestive heart failure (CHF). Specifically, this particular device is “good for” long-term monitoring of CHF patients. An appropriate test of it would see large numbers of patients implanted with the device for long periods of time and parameters like hospitalization rates and life expectancy measured. Yet, before exposing many patients to new technology over long periods, you had better conduct a more limited clinical trial. In this trial you would demonstrate in a small group that the device can be implanted safely and can function after implantation. Only after making your point in a relatively small study will you go on to conduct the larger trial meant to test the device’s intended use directly. Now this sort of early trial will provide a great deal of information on the product’s functioning and very little about its clinical benefit. But it is necessary before embarking on a study designed to test “what it is good for.”

Another example is the dose-response studies in pharmaceuticals where each group receives a different dose of the same drug (and a dose = 0 condition is usually included as well). In this sort of study you aim to identify a drug’s optimal dose rather than addressing the general “What is it good for?” Once the dose has been established, you can go on to test the product’s intended use.

1 Your initial study will likely have a short follow-up (say, two or three months), after which, if you succeed, you will go on to the larger trial with the longer follow-up (say, a year to two). At the same time, you will continue to monitor those patients from the first trial. You do not, however, want the initial trial to extend over a year or two, since this will greatly delay time-to-market. Just how long the initial “short and limited” trial ought to be is something to be discussed and decided upon with clinicians and regulators.

2 There can, of course, be dose-response relationships of interest in devices as well. For example, when using a cardiac catheter for ablating (burning) by electrical current, there will be a relationship between the current’s strength and the degree of ablation. You may then wish to conduct a study to determine the optimal “electrical dose” for a given application.
Thus, long before you reach the pivotal trial stage—the study or studies determining whether your product should be offered to the general public— you will need to address numerous preliminary issues.

Product development, by definition, takes place over time. In our particular industry much of the process is formalized with many conventions, including specific names for processes and stages. Thus, there are preclinical studies where your product is assessed in the laboratory and clinical trial Phases I, II, and III where your product is tested on humans. There are many variations on this broad scheme, and few development programs are staged exactly alike. Regardless, the “What is it good for?” question will only be answered definitively at the very end. Thus, when planning a specific study, you would do well to come up with explicit questions tailored for the specific trial at the particular stage. And the question most appropriate to begin with is “What do I want to show in this trial?”

Now this particular question has some very definite implications in the context of a given study. At the same time, you would do even better to subdivide it into the following two issues:

1. “What attribute of my product do I want to assess?”
2. “What about this attribute do I want to show?” That is, what do I aim to demonstrate with this attribute that I have chosen to assess?

In this chapter I cover the most common attributes tested in clinical trials. In the next I will enumerate goals you might set for these attributes—that is, what you would like to demonstrate about them. Finally, I will put the two together to create a sort of “matrix guide” to defining clinical trial objectives for clinical trials in general.

**ATTRIBUTES**

**Efficacy**

For a product to be “effective” it must do what it is meant to do. Simple. A blood test assessing a woman’s risk for having a baby with Down syndrome should be accurate, and a pill for reducing pain should do just that.

Defining a product’s efficacy is really another way of answering the question “What is it good for?” This then seems to bring us back to square one: when I said that “it is often much too general to be of practical use when planning a particular clinical trial.” Well, I do not retract.

First, “often” is not “always.” Second, as I showed in the preceding chapter, a product’s ultimate use is not necessarily that assessed in a given stage of development. Finally, and perhaps most importantly, issues in clinical
development will sometimes weave within and upon themselves, taking you back to places you have already been. Testing efficacy is only one of numerous attributes that a trial might assess. And it may or may not be a relevant question, depending on the phase of development you happen to be in at the moment.

**Safety**

If an effective product does what it should do, a safe product should not do what it is not supposed to do. For example, a drug for relieving migraine headaches should only relieve migraine headaches. It should not cause annoying side effects like fatigue or disorientation or any other bodily reaction apart from its intended effect.

To take a more complex example, some medications for autoimmune disorders, such as multiple sclerosis and rheumatoid arthritis, are designed to suppress one or another of the immune system’s responses. More particularly, they aim...
to restrain that activity of the system that is most damaging in the disease—the specific immune reaction causing the system’s misguided assault on the patient’s own organs. But suppressing immune activity has its risks, not least of which is weakening the body’s ability to defend itself from real threats. Thus, in the case of immunosuppressive agents, an important element in demonstrating safety is showing that while protecting the body from one kind of disease, it does not expose it to others.

ON THE CONSUMPTION OF CAKES

Now most pharmaceuticals and interventional device products are not completely safe, and you will rarely get efficacy without exposing the physiological system to some risk. As in life, having your cake and eating it too is a virtual impossibility. And while we are spouting clichés, I might also mention that there is no free lunch. Given these alas-too-true life principles, demonstrating safety often involves showing that a product’s benefits outweigh its risks. In other words, rather than showing your product to be perfectly safe, your goal when assessing an attribute or combination of attributes is showing that the product is worthwhile “all things considered.” This naturally leads to a risk-benefit analysis that is a section typically included in clinical trial reports.

Risk-benefit analysis need not limit itself to considerations of the safety-efficacy tradeoff alone. The section will often deal with issues external to the product, such as alternatives to it, cost, and the severity of the illness it treats. We would expect, for example, that physicians who are treating aggressive life-threatening illnesses will be more concerned with efficacy than safety relative to those who are treating minor ailments. Thus, the tradeoffs between any product’s attributes must be considered in the wider context of the disease it treats, the intended use population, and other relevant factors.

Performance

In clinical trials, the term performance has been used to refer to different attributes. In this book I shall limit its use to refer to “manipulation”—that is, to operating the product successfully. To function properly some medical products require manipulation beyond relatively simple actions like swallowing a pill or injecting medication into a patient’s arm. This issue is often encountered in interventional devices, such as surgical apparatuses or catheters meant for insertion into blood vessels.

For example, there have been a number of surgical techniques developed for eliminating uterine fibroids—benign growths in the uterus that can cause great discomfort, heavy menstrual bleeding, and infertility. A necessary but not sufficient condition for effective treatment is performing the specific surgical technique correctly. This can be assessed during the surgery itself or soon after. Evaluation of efficacy—assessing the ultimate goal of surgery of relieving the physical and psychological difficulties caused by fibroids—could take many months and even years to do properly.

To evaluate performance in uterine fibroid removal, you might measure the time it takes to conduct the procedure, its ability to remove the fibroid
completely, and whether the procedure requires a particularly adroit surgical manipulation or can be done with average surgical skills only. Additionally, you may want to assess the degree to which the procedure can be done without affecting the tissue around the fibroid.

Note that none of the parameters mentioned in the preceding paragraph involve efficacy directly in the sense of evaluating the procedure's intended effect on the patient's ailment (e.g., its ability to reduce pain or menstrual bleeding). Performance is related to efficacy in that you must succeed with the former to achieve the latter. Yet the two are distinct in that acceptable performance is a necessary but not sufficient condition for efficacy. Not only should an operation succeed, but it is also recommended that the patient live. And because performance and efficacy do not completely overlap, they are often evaluated separately—in the same or different studies.

The term *performance* is also used to describe the physical aspects of the product itself. For example, many products are required to withstand a minimal force before breakage and/or be provided in sterile packaging. For these aspects of performance the manufacturer might be asked to test both the product's strength and the integrity of its packaging. Clearly, products of which the sterility may be compromised by faulty packaging and/or are likely to break when used should not be on the market. Such physical attributes of products are critical for both safety and efficacy, but they are usually not tested in clinical trials. Physical performance of products is usually evaluated in *bench testing*, which typically involves assessing products in laboratory environments. Thus, for example, the strength of a guide-wire used in catheterization might be tested by stretching it to the breaking point while measuring the force applied. The force at which the guide-wire tears is then specified as that which it can withstand. You would then compare your results to acceptable standards for such products, determining whether your guide-wire's strength complies with that required.

Another use for the term *performance* relates to subject compliance with medical treatment. For example, a pill may be effective chemically, but it is useless if subjects are unwilling to take it for one reason or another (e.g., hard to swallow, must be taken too often, etc.). Here, too, performance—compliance—is a necessary but not sufficient condition for clinical efficacy. As noted at the beginning of this section, I will limit my use of the term *performance* to the assessment of the degree to which a medical product can be manipulated successfully.

---

3 If, for example, breakage of the tested device occurs in a clinical trial, it will certainly be recorded. But it is unexpected, and the trial is not set up for this. Typically, a clinical study will be approved only after you have shown that the physical attributes of the product are acceptable.
Pharmacokinetics

Pharmacokinetics is the study of what a body does to a drug: the rate at which it is absorbed, the time it reaches its maximum concentration in the body, the time it takes to be eliminated from the body, and so on. For example, you may want to measure quantities of the active ingredient in the blood over time for an orally ingested drug and compare these quantities to the same drug administered intravenously. Other parameters of pharmacokinetic interest may be the drug’s behavior when given in different formulations and doses, when administered before meals or after, and so on.

Like performance, a drug’s pharmacokinetics profile is related to efficacy but distinct from it. Thus, a formulation will not be effective if it cannot be absorbed by the body and distributed properly. Yet, absorption does not guarantee efficacy. The latter has as much to do with the efficacy of the drug’s active ingredient as with its kinetics.

Virtually all medications require some sort of pharmacokinetic analysis as part of the development process. At the same time, pharmacokinetics is especially central when dealing with generic drugs—medications that are copies of brand name drugs (sometimes erroneously termed ethical drugs) that are produced once the original patent of the latter has expired. In most cases, approval of generic drugs involves demonstrating that their pharmacokinetic profile is equivalent to that of the original. In other words, generic drug producers are usually not required to conduct clinical trials for demonstrating efficacy. Such trials have already been conducted for the original drug, and what remains for generic producers to show is that theirs behave similarly in the body. The regulator reasonably assumes that if a generic drug is similar chemically to the original and behaves in the body similar to the original, it will also yield similar clinical outcomes to the original. Chemical similarity is shown through the production process itself, and behavior in the body is tested by comparing the pharmacokinetics of the generic and original drugs.

There are, however, exceptions. For example, topical drugs—those used on the skin or other external parts of the body—often do not enter the bloodstream, or they enter in quantities too minute to evaluate. As such, they are not assessed on pharmacokinetics (or assessed to ensure they do not enter the blood in detectable quantities). Here, a generic drug maker may have no choice but to conduct a clinical trial to demonstrate that the new drug’s efficacy and safety are equivalent to the old.

---

4 Ethical drugs refer in general to those that can only be given by prescription. In clinical trials the term commonly refers to a branded drug under patent protection.
CHAPTER 3: Medical Product Attributes

SUMMARIZING AND SOME THOUGHTS

Before going ahead and planning your clinical trial you must be clear on the choice of attribute your study should evaluate. There are several to choose from. The most common are efficacy, safety, performance, and pharmacokinetics. These cover the majority of attributes you will encounter when assessing clinical products. Yet, there are others, and we shall make a note of them from time to time.

At the end of the day you will want to know what your product is good for, which is really another way of asking if it is effective. Thus, of the attributes enumerated, efficacy is typically most directly related to your ultimate goal. For example, patients suffering from rheumatoid arthritis (RA) will buy your product if it reduces pain and swelling and enables greater freedom of movement. At the same time, they will certainly expect your drug to be safe, so demonstrating adequate safety is critical to any medical product.

It would seem then that of all the attributes enumerated, efficacy is most directly related to the more general "What is it good for?". This is in fact the case. Yet, determining the attributes to be evaluated must be examined on a study-by-study basis. This is especially true in early development, where there is a great deal to be understood about a product in addition to its efficacy. For example, in some cases you might wish to launch your product as quickly as possible, even if this means marketing less than your final version for it. This in turn would imply a more limited trial—one that evaluates less than the ultimate "efficacy package." You might, for instance, have a diagnostic kit meant to measure breathing rate, heart rate, sleep apnea, and sleep stages. Now it is relatively easy to recruit subjects for testing, say, heart and breathing rates—all subjects have them. But recruiting subjects with sleep apnea will be more difficult and is likely to lengthen your trial and delay regulatory submission. As a result you might choose to conduct a clinical trial assessing your kit's ability to measure breathing and heart rates and leave the "apnea submission" for later. In this particular case you will have tested only a subset of "what the product is good for." Another reason for testing only a subset of a product's (planned, final) efficacy may be that your R&D people are ready to sign off on one of the product's attributes but feel the need for more time to perfect others.

So while the question "What do I want to show in this trial?" is typically related to "What is my product good for?," it often also differs from it in any particular study. And this difference—be it small or large—will have some very definite implications for what you expect your study to achieve. This in turn will influence many aspects of your trial, including its design.

It is therefore vital to emphasize that when planning trials you should not, at least initially, consider any one attribute more important than another. First, the regulator often views your attributes' importance differently than you do.
Second, the attributes enumerated are related to one another, so it may be artificial to rank their importance. For example, a surgical device with inferior performance characteristics is likely to be ineffective and unsafe as well. Similarly, few people will be willing to take a medication that frequently produces unpleasant side effects, even if it is approved. It will thus be ineffective in practice even if its active ingredient is, in principle, very effective.

To the statistician, safety and performance and pharmacokinetics sometimes feel like adjuncts to efficacy. Physicians, on the other hand, will typically raise the safety issue before all others. Since both safety and efficacy are important, as are pharmacokinetics and performance, personal preference in prioritization is somewhat beside the point. All must be tested before a product is to enter the market.

**A FINE LINE CRISSCROSSED**

Science has gotten us far. We now, for example, treat diseases like diabetes that once meant certain death. Additionally, we have developed fantastically complex and informative diagnostic techniques like computer tomography (CT) and magnetic resonance imaging (MRI). In developed countries life expectancy has increased dramatically in the last 100 years, and a large part of the credit resides with medicine. Moreover, at any given time scientists, clinicians, and entrepreneurs are continually working to provide us with newer and better products. We expect no less. And we want these products to be safe and effective, which they generally are. But not so fast—or, perhaps, even faster.

Let me explain: If you want to know the long-term effects of a drug, you will, alas, have to study it in the long term. Thus, you cannot really know whether an innovative drug is safe when taken over 10 years until you have tested it for this long. But if you wait 10 years before bringing it to market, you will have kept it from some very eager patients (not to mention the possibility of having gone bankrupt in the meantime). Similarly, when developing a vaccine you cannot really know how well it works without giving it to thousands of people and following up on them for months and even years. Yet, there are times when a vaccine is required on short notice, such as, for example, when a new strain of flu threatens to create an epidemic. So instead of testing the long-term effect of the product, you might test whether the vaccine produces the antibodies for the disease in question. Thus, many vaccines introduced to market have not had their intended use tested directly, nor will they have had their long-term safety assessed.

What are we to do? As a society we want innovation quickly, and we (and our lawyers) want these innovations to have positive effects only. Well, you cannot have both. And in the short history of biomedical development and regulatory approval there are numerous examples of drugs and devices approved that were later found harmful. This is a sad state of affairs. But there is really no way around it; while we might be able to improve the system of innovation and regulatory approval, the tradeoff between speed and safety has, in principle, no solution. The best you can do is design a process optimizing the two—creating a system of checks and balances that will yield innovation with “reasonable” speed while providing safety with “reasonable” assurance. You will then continually monitor the process and tweak it as necessary. And this tweaking will often come after discovering that a product reached market when it should not have.

Unfortunately, I have nothing original to propose here. I merely wish to point out that as long as people demand “new products now” and get them, they will also, from time to time, end up with products that are not as safe as they would like. So the next time you hear about an approved product turned sour, do not be quick to judge the regulator harshly. We—consumers, physicians, legislators—have placed agencies such as FDA and EMEA in a bind from which they cannot extract themselves to everyone’s satisfaction. The line between speed and safety is a fine one, and “to approve or not to approve” is precisely the question. All decisions on approval come with their risks and rewards, costs and benefits. And, on occasion, the regulator will find itself on the wrong side of the line.
In sum, to get your product approved by regulatory authorities, prescribed by physicians, and purchased by customers, you will need to show that it possesses a reasonable combination of the attributes relevant for it. And to assess these attributes you will usually be required to conduct one or more clinical trials. To plan any trial correctly, you must know in advance what your product is good for in general and what you aim to show in the particular study. And while these issues overlap, they are not necessarily the same. This is sufficiently self-evident that it had better be put in writing.