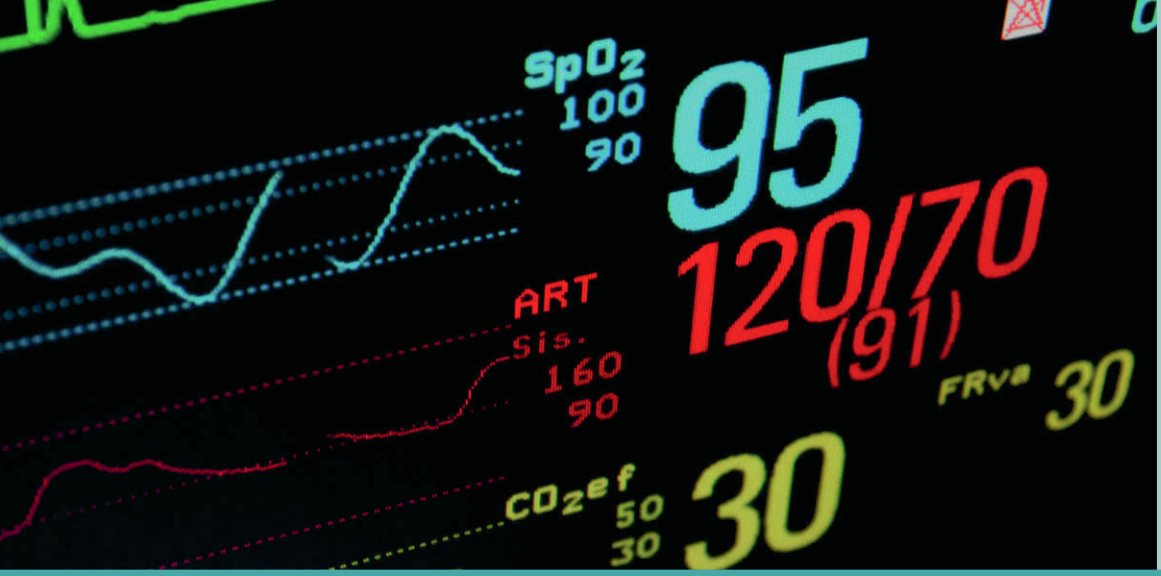


# 5.3 Clinical Strategy

## INTRODUCTION

*Human device testing is at the pinnacle of the medtech innovation process. The stakes are high: Two to three years to perform patient recruitment, enrollment, investigation, and follow-up. Costs as high as $100,000 per patient studied. Regulatory approval and reimbursement hanging in the balance. The credibility and commercial viability of the company on the line. And, most importantly, patient lives at risk. These are the types of issues that make clinical device testing a risky and challenging (yet essential) undertaking. An effective clinical strategy not only provides a mechanism for innovators to plan and initiate human testing, but to optimize its overall approach to clinical development.*

**OBJECTIVES**

- Recognize the importance of establishing an overarching clinical strategy for early preclinical and human clinical studies.
- Appreciate the different types of clinical studies and how their designs relate to the overall goals of clinical development (including regulatory, reimbursement, and market adoption considerations).
- Learn the process of planning a human clinical trial.
- Understand tactical considerations for developing safe, cost-effective, and statistically robust clinical trials.

In the context of the biodesign innovation process, clinical trials are broadly defined as human studies performed to determine specific outcomes based on the use of a new medical technology. Traditionally, the objective of clinical trials has been to demonstrate that a new device offers measurable, clinically important benefits to patients in terms of its effectiveness and safety.[1] This evidence is essential to supporting the regulatory approval of the device. However, the complexity of clinical development has changed dramatically over the last 15–20 years. Trial data are now commonly required to demonstrate clinical value to patients and financial value to payers as part of reimbursement pathways. Similar data are also required to address physician interests and concerns in order to drive market adoption. Because it can be difficult to design a single study that is capable of meeting all necessary regulatory, reimbursement, and marketing endpoints, innovators are often advised to think about study design as part of a larger clinical strategy that includes a progressive series of trials to achieve the company's overarching goals. However, the downside of this approach is that clinical trials are often the most costly and complex activity a start-up will undertake, and conducting multiple studies can strain the resources of even the most promising project. An effective clinical strategy must therefore define a clinical pathway that addresses the company's top priorities in a realistic manner.

The creation of a medtech clinical strategy begins in parallel with research and development (R&D) since the clinical development pathway must be tightly integrated with device engineering (see 5.2 R&D Strategy). In addition to maintaining a tight linkage to R&D, an effective clinical strategy must be synchronized with the other strategic work streams in the development stage – see 5.4 Regulatory Strategy, 5.6 Reimbursement Strategy, 5.7 Marketing and Stakeholder Strategy, and 5.8 Sales and Distribution Strategy.

See ebiodesign.org for featured videos on clinical strategy.

## CLINICAL STRATEGY FUNDAMENTALS

Every innovator strives to develop a medical innovation that ultimately addresses the defined clinical **need**. Clinical studies, performed as part of a comprehensive clinical strategy, provide the evidence necessary to ensure that the new innovation is safe and effective.

Clinical strategy defines a prospective approach through which the organization can anticipate and manage the clinical risk associated with the project. A well-developed clinical strategy also helps ensure that clinical activities are tightly coupled with other important efforts underway within the company as part of the biodesign innovation process. No longer can innovators think of products as simply requiring development and testing. Rather, through the clinical strategy, they should seek to integrate testing into the development plan as a series of **value** building steps that ultimately result in a technology that addresses a clear clinical need and satisfies regulatory, **reimbursement**, and market requirements to positively impact patients.

Innovators and companies often feel both excited and apprehensive as they prepare to execute **clinical trials**. In recent years, the requirements for clinical data to address regulatory, reimbursement, and adoption concerns have become increasingly stringent and continue to grow more complex. According to Frank Litvack, former chairman and CEO of Conor Medsystems:[2]

> *The complexity, size, and expense of clinical trials for important medical devices are going to do nothing but get bigger before they get smaller. And I think that has implications for everybody who's in the start-up business. It means it's going to take longer and you're going to need more money. And there's going to be more risk. That's just the world in which we live.*

For innovators developing new medical technologies, clinical trials are often the largest line item (by far) within their preliminary, pre-revenue budgets. Early in the innovation process, generating trial data is absolutely essential to attracting talent and funding to the project, but teams can often struggle to cover study costs, even on a relatively small scale. Consider Respira Design, a team from Stanford University that developed an asthma spacer for use in resource-constrained settings such as Mexico (where the students conducted their needs finding exercise). "We were focused on achieving best possible quality at the lowest possible cost," recalled Santiago Ocejo, one of the company's founders.[3] After benchmarking the make-shift solutions physicians used to help deliver asthma medication to the lungs of their pediatric patients, he explained, "Our cost benchmark was the price of a plastic soda bottle." The Respira team's innovative solution is a spacer produced from a single sheet of paper so it can ship and store flat and then be transformed into a usable device through a series of cuts and folds (see Figure 5.3.1). Despite the simplicity of the design and its low cost to produce and distribute, the team needed to collect clinical data to obtain regulatory clearance for the device. These data would also be used to demonstrate safety and effectiveness to physicians and patients, so the team felt an imperative to understand the extent to which the product impacted the delivery of asthma medication, how many uses each device could sustain, and whether the spacer would function as

FIGURE 5.3.1
The Respira asthma spacer being used by a young patient in Mexico (courtesy of Respira).

intended in situations of emergency or distress. "This was a medical device that would potentially be used for someone who was having an asthma attack," explained Barry Wohl, another co-founder. "We couldn't put it in the hands of a mother to treat a child without a detailed understanding of how effective the device was in transferring aerosolized particles from the inhaler to the lungs. That was the minimum amount of clinical data we needed to be able to sleep at night." To conduct the necessary tests, the Respira team needed substantial funding. Unfortunately, Ocejo, Wohl, and their third co-founder, Eric Green, quickly discovered that potential donors and investors alike wanted to see clinical data showing that the device worked before making a sizable financial commitment. Ultimately, this quandary was one of the factors that stalled the development of the solution. "Cost was on our radar from the beginning, in terms of materials and distribution," said Green. "But we didn't realize how expensive testing would be." The team cautioned other medical device innovators to plan carefully and proactively for the time and expense associated with gathering user data in a safe and ethical manner, even for relatively simple, straightforward technologies.

For more complex technologies with a higher risk profile, the burden of generating clinical data can be even more daunting. As regulators, **payers**, and practitioners demand data from larger trials conducted over longer periods of time, clinical activities take longer to complete and are more complicated and costly to plan and execute, especially for truly novel technologies. Companies not only must raise the resources to fund the trial themselves, but also must cover their monthly cash expenditures, which can be significant as the technology nears the market. The two-part story on a company called Emphasys Medical illustrates the stress this can place on a start-up organization (see part one at the end of this chapter and part two in 5.4 Regulatory Strategy). A well-constructed clinical strategy helps innovators anticipate and manage the growing challenges associated with clinical testing.

Before diving into the detailed overview of clinical strategy development and tactical trial planning that follows in this chapter, it is important to emphasize the ethical responsibility that innovators assume when initiating clinical evaluation. Individual innovators and companies alike must commit themselves to the ethical treatment of all animal and human **subjects** involved in their studies and use this commitment to guide the development and implementation of a clinical strategy. Care should also be taken to avoid conflicts of interest and other ethical dilemmas that have the potential to negatively affect actual (and perceived) study results.

## Clinical study goals

The development of a clinical strategy begins with the definition of the objectives (desired outcomes) of the strategy and of the studies that the company intends to undertake. One of the first questions innovators should ask themselves is, "What is the indication for how the solution will be used in practice?" Far too often, lofty goals result in a strategy that targets an overly ambitious indication before the innovators deeply understand the strengths and limitations of their solution. Although single clinical studies with large market indications are appealing to investors when reviewing a business plan, a clinical trial strategy comprising a series of studies with expanding indications has a far greater likelihood of being successful.

A team's objectives can be achieved progressively – it is not uncommon for a project or company to stage its studies based on its strategy. For example, trials with specific objectives (regulatory, reimbursement, or

marketing) are synchronized with the milestones in a company's operating plan such that the data generated by the trials become available as they are most needed (see 6.1 Operating Plan and Financial Model). Implantable cardiac defibrillators (ICDs) provide a good example of a staged approach to clinical testing. Initially, ICDs were studied and approved for use as a form of secondary prevention in patients who had experienced cardiac arrest due to ventricular fibrillation. However, after this approval, the MADIT trial demonstrated that patients with a history of coronary artery disease and heart pump dysfunction could benefit from ICDs as a form of primary prevention (i.e., even if they had not yet experienced a cardiac event caused by ventricular fibrillation).

Within this framework, innovators should next ask themselves questions such as: "What results are needed to support regulatory approval? Are economic outcomes important to support reimbursement decisions? Will data be necessary to help market the device to physicians and/or patients?" Ultimately, the design and execution of each clinical study will be based on the answers to these types of regulatory, reimbursement, and marketing inquiries.

*Regulatory considerations*

For the large majority of medical device clinical studies, regulatory considerations are the primary drivers of trial design. (Basic requirements for the two primary regulatory pathways in the US – **510(k)** or **PMA** – are described in 4.2 Regulatory Basics. More strategic regulatory considerations are addressed in 5.4 Regulatory Strategy.) Usually, a final trial design will result from a negotiation between the company and a given regulatory agency. Whether dealing with a **Notified Body** as part of the European Union **CE marking** process, the US Food and Drug Administration (**FDA**) or another regulator, these regulatory agencies try to base their decisions on prior experience with similar technologies, as well as changes in science and the practice of medicine over time. In certain areas, the interests of the company and the agency are aligned with regard to the details of the trial design; that is, both parties want to achieve valid data that will be publishable in high-quality medical journals, while providing maximal safety to the research subjects who participate in the trial. However, the company has the additional imperative to achieve an endpoint that is favorable to the product, as quickly as possible, and at the lowest possible cost to deliver value to its investors.

*Reimbursement considerations*

Increasingly, medical device trials are being designed to provide cost-effectiveness outcomes and economic evidence for attaining reimbursement (particularly from the Centers for Medicare and Medicaid Services (**CMS**) in the US and technology assessment authorities outside the US – see 5.6 Reimbursement Strategy). This may include the incorporation of a formal cost analysis into the trial, along with measures of the financial impact of the outcomes and stricter endpoints than regulatory agencies normally require. On the upside, these requirements can lead to more rigorous trials that result in more robust data and more formidable barriers to entry for competitors. However, they also make trial design more complex since the desired outcome is not only to demonstrate the safety and efficacy of the device (as required by the FDA, for instance), but also to show equivalence or superiority to an existing technology or procedure on the market, as this latter outcome is often necessary to justify reimbursement.

*Marketing considerations*

A third objective of many clinical trials is to generate data that help give the new technology an optimal launch in the marketplace. Such marketing considerations can have a major impact on trial design. It may be that the physician group targeted by the new technology will be most convinced by a certain type of trial – for example, a **randomized trial** that compares the new technology to a current standard of practice. Or, if there is a choice to test the technology in different patient groups, it may be advantageous from a marketing standpoint to target a certain population (e.g., younger patients who are willing to pay directly for the technology and, thus, provide an early revenue stream for the company). The choice of which investigators to include in the trial can also be important. Companies frequently pursue investigators from among "marquee" physicians and key opinion leaders (**KOLs**) – high-profile practitioners who give talks frequently and are influential among their colleagues (see 5.7 Marketing and Stakeholder Strategy).

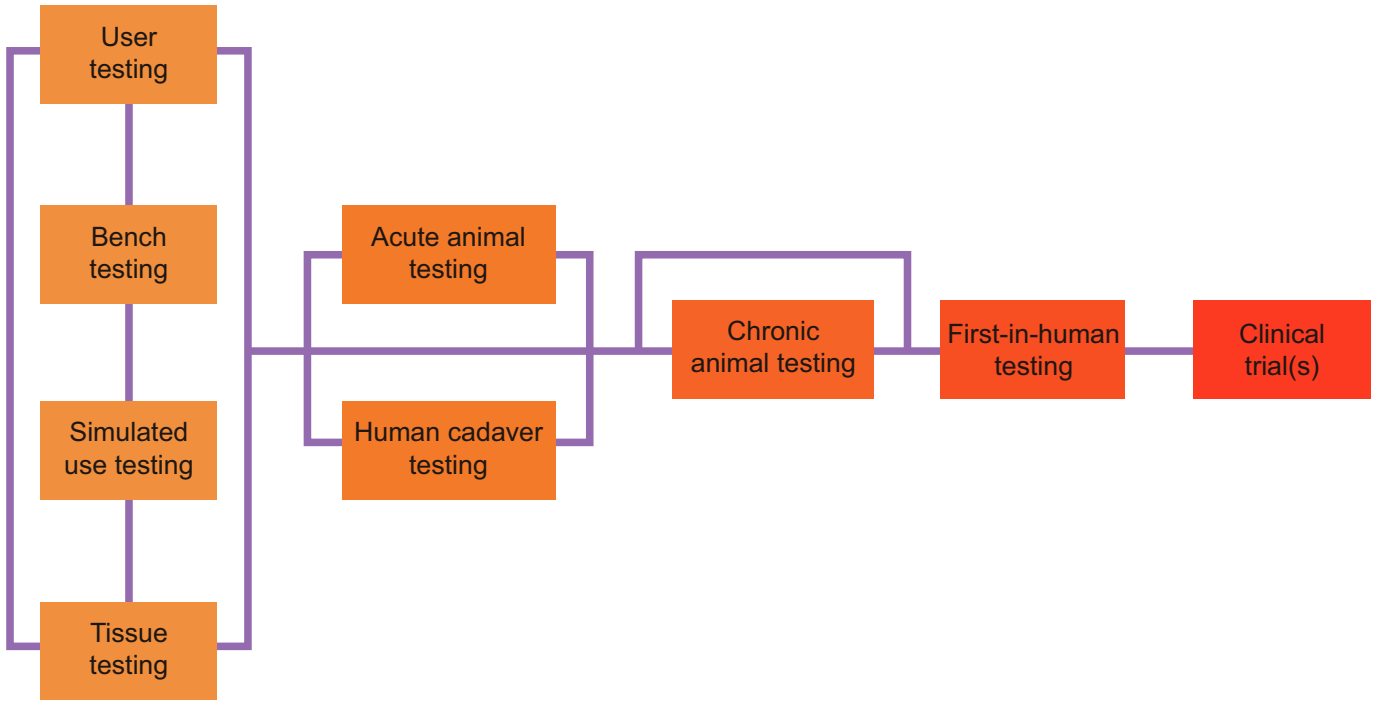


FIGURE 5.3.2
The biodesign testing continuum includes preclinical and clinical studies. Recall that not all tests are required as part of every project and should be determined based on the characteristics of the technology.

## Preclinical and clinical evaluation

**Prototyping**, device R&D, and preclinical animal studies often overlap, with the boundaries for where one begins and another ends varying significantly from project to project. To help make sense of how these efforts interrelate, one can think about the steps in the biodesign testing continuum (see Figure 5.3.2; originally introduced in 4.5 Concept Exploration and Testing) as generally corresponding to two different types of efforts: preclinical and clinical studies. Preclinical studies begin with basic prototyping and continue through chronic animal tests. The focus of early tests is to assess feasibility through user, bench, simulated use, tissue, and cadaver testing or acute animal studies. Later, testing usually involved **hypothesis**-driven studies in animal models that primarily seek to evaluate safety, but sometimes also can provide insights into the potential efficacy of a device. Clinical studies involve human device testing for the evaluation of specific outcomes, which often include both safety and effectiveness.

### *Preclinical studies*

The studies performed during concept exploration and testing (see chapter 4.5) are part of preclinical testing. When a company seeks to answer critical feasibility questions that extend beyond the prototyping of basic device functionality, it typically extends its preclinical efforts into ex vivo human cadaver or live animal testing. Usually, preclinical live animal tests are performed as acute animal studies. In vivo animal tests enable researchers to perform a preliminary evaluation of whether or not the device will function as desired in a living system. For example, an ablation catheter might successfully destroy tissue in simple tissue tests (i.e., using steak as a proxy for heart tissue and/or animal hearts from a butcher). However, until the device is placed in a living system, the inventor cannot be certain regarding fundamental device feasibility (e.g., is the device able to reach the correct anatomic area? Does its interaction with the animal's blood affect the device's ability to effectively ablate tissue?).

**Acute animal studies** An acute animal study is often an ideal method for evaluating device feasibility. These studies are performed in order to answer a specific, important question and then the animal is euthanized immediately following the test. Acute animal studies allow researchers to assess the device in a small, finite number of living systems prior to accepting the risks and expense of initiating a more extensive, systematic preclinical study. As with any animal study, researchers must be certain to apply for approval in advance of performing the tests, and should adhere to defined protocols for the ethical treatment of animals (see the section "Institutional Animal Care and Use Committees" for more information).

The first step in initiating any in vivo animal testing is to establish if an animal model of the human disease or disorder exists. If multiple animal models have the potential to provide a viable test, then consider secondary factors such as what animal models have been used by similar existing technologies in the past. For instance, there is a long history of using a swine model for evaluating coronary stents. However, not all models are this straightforward. No animal model may be available for an obstetric device due to the unique characteristics of the human pelvis and the high hormone levels experienced during pregnancy.

**Chronic animal testing** Once researchers have successfully addressed critical issues related to device feasibility through acute animal studies, they can transition into more systematic preclinical studies, such as chronic animal testing. In contrast to the acute animal studies, which are primarily focused on the viability of the technology, chronic animal studies typically involve larger numbers of specimens and seek to prove or disprove a specific predefined hypothesis in small or large animal models (e.g., mice or pigs, respectively). The safety and effectiveness of the device also become important objectives since the overarching purpose of these experiments is to gather evidence to justify research in human subjects.

Given the emphasis on safety and effectiveness, animal survival is almost always included among the important endpoints in a chronic study. Careful attention to analgesia and post-operative comfort and mobility is essential. Methods for monitoring the animals must be established and procedures defined for ethical euthanasia for any animals that are suffering unduly, regardless of how this affects study outcomes.

**Working Example**

**An overview of institutional animal care and use committees**

According to US federal law, any company or institution that uses laboratory animals for research or instructional purposes must gain approval from an Institutional Animal Care and Use Committee (**IACUC**) prior to beginning research. The purpose of the IACUC is to oversee and evaluate all aspects of the company's animal care and use program. Such a committee is assembled by the institutions performing animal testing and often includes administrators, veterinary experts, and members of the public. All research and teaching activities involving live or dead vertebrate animals must be reviewed and approved by the IACUC before a study is launched. Approval is obtained by submitting a protocol, which establishes the reason for the study, justification for why an animal study is necessary to evaluate the medical problem, and the processes put in place to ensure the ethical treatment of the animals in the study.

Importantly, over the last decade, the intensity and quality of IACUC oversight has evolved substantially. Members of the committee are experts dedicated to both the safety and comfort of the animals, as well as the quality of the science resulting from the trials. The committees themselves are under careful, routine scrutiny by government agencies.

It is worth noting that many members of the public have grave ethical concerns about animal experimentation. Keep in mind that this may include members of the development team. Importantly, all other options for testing a device must be fully explored before any animal is caged, anesthetized, operated on, or potentially sacrificed. Furthermore, it is essential to have a discussion about these issues prior to conducting animal tests to allow any team members with ethical objections to voice their concerns and opt out of the studies.

An important challenge associated with chronic studies of healthy animals is that it can be difficult to get an accurate prediction of device performance compared to the case of a patient with a disease, several comorbidities, and/or advanced age. In some situations there are disease models in animals that have been developed to mimic at least some aspects of the human condition. For example, pig coronary arteries can be pre-treated to create narrowings that are angiographically similar those seen in humans. The tissue composition of these lesions, however, is substantially different than the plaque that builds up in human coronary arteries. As a result, extrapolating device performance based on this animal model has limited utility. In general, there is wide variation of the comparability of disease models in animals to the corresponding human condition – and this can be a major factor in determining the time, effort, and money that a team chooses to invest in this type of testing (refer to the Emphasys case later in this chapter).

Although not common, some preclinical studies look beyond safety by seeking to statistically establish the efficacy of a particular endpoint. **Efficacy endpoints** are selected and then placebo or "sham" procedures (designed to simulate the risk of the device procedure without providing active therapy) are used to analyze the effectiveness of a device treatment. These tests require careful attention to design since the data are only of value if the animal model reflects human disease characteristics and if the endpoint chosen is meaningful for a human study. For example, if the goal of a new device is to improve heart function through the transplantation of stem cells into an injured heart, efficacy could be evaluated by examining the change in pumping function following cell transplant. In this example, an injection of saline could be used to assess the effect of the injection alone, while the difference between the effect of the injection of saline on heart function and the injection of stem cells on heart function could be used to evaluate stem cell efficacy. Having a clearly defined clinical strategy in place prior to embarking on device testing helps ensure that researchers choose the most appropriate endpoint for each preclinical study. This can help them to maximize the value of the data when it is time to transition into human trials.

The demonstration of safety is essential for obtaining approval for **first-in-human** testing. Chronic animal testing, although limited, provides some of the strongest evidence for safety in support of a first-in-human ethics committee submission. These data can also help establish the potential clinical value of the device so that physicians are willing to enroll patients in the study. Additionally, they expand the researchers' base of knowledge so that the probability of causing harm to patients (or of not meeting desired endpoints) is reduced.

**Working Example**

An overview of good laboratory practices

When conducting preclinical studies, researchers must determine whether or not to follow a research standard called Good Laboratory Practices (**GLP**), as defined by the FDA. In essence, GLP is a set of guidelines that describes in detail how studies should be performed and data collected. The FDA requires that data generated to support a 510(k) or premarket approval (PMA) submission be gathered according to GLP standards. The guidelines specify minimum standards for safety protocols, facilities, personnel, equipment, test and control activities, quality assurance, record keeping, and reports used in conducting the trial. GLP also requires the laboratory to have an extensive written set of operating guidelines (called standard operating procedures or SOPs – see 5.5 Quality Management) for conducting the study. Regulatory agencies outside of the US do not require companies to follow GLP standards; however, they may insist on adherence to **ISO** standards for their study submissions.

Importantly, not every preclinical study needs to be conducted in accordance with GLP guidelines. Although GLP standards ensure robust results, early studies that are performed to assess feasibility or even answer questions of safety do not require such rigorous standards, which can be time-consuming and add increased expense to the project. Synchronization of the clinical strategy with the company's developmental timeline will help establish the need for GLP studies to support key milestones.

*Human clinical studies*

Progressing from preclinical animal studies to human clinical studies represents a major milestone for most device companies. The opportunity to test and evaluate a new medical device in a human is both an opportunity and risk. Medical devices that fail in a human (or, more importantly, harm a patient) are unlikely ever to be used again. Several different types of studies can be performed for human device testing, depending on the nature of the device, the clinical problem being addressed, and the stage of testing. Each study type may provide an opportunity to further advance the technology (see Figure 5.3.3).

**First-in-human studies** Before a company can initiate large-scale clinical studies, it first must complete first-in-human studies. The most important outcome of these small-scale, preliminary human studies is safety, although investigators are also looking to see whether the device performs as intended (even though a specific efficacy endpoint may not be defined). Because first-in-human studies are not designed to establish a clinical benefit, efficacy is anecdotal. Careful thought must be given to the appropriate time and place to perform first-in-human studies, given their significance. Ensuring that the device design has been optimized for human anatomy will improve the researchers' chance of success and minimize the risk of causing harm. There are many reasons that may explain device failure in early human studies, but it is often due to too much reliance on prior animal studies in which the organ or system was overly forgiving and free of disease. This risk can be minimized through the careful evaluation of human anatomy and human cadaver studies as part of the clinical strategy.

**Registries and observational studies** A **registry** is a collection of cases performed in a real-world setting (rather than patients treated in a specifically designed comparative study), which may be accumulated either prospectively or retrospectively after a number of cases have been performed. Prospective registries are also called "**observational**" studies and are often used in the pilot phase of testing a new device – typically, the first 10–100 cases following first-in-human tests where the company, investigators, or the regulatory agency may be attempting to learn enough about a device's performance to design a definitive trial. Registries from overseas, for instance, have recently been used in support of 510(k) applications in which the burden of clinical proof is modest (i.e., the device is known to be comparatively safe).

FIGURE 5.3.3
Human clinical trials can take many different forms, but all require careful planning and the highest of ethical and safety standards (courtesy of ExploraMed).

An increasingly important use of registries is to monitor the outcomes of a device after it is approved by a regulatory body and as it is launched into more widespread clinical use. This approach has resulted from recent, high-profile examples of devices that showed unanticipated complications following an approval (e.g., implantable cardioverter defibrillators, drug-eluting stents). Registries are generally much less complex and expensive than randomized trials, but have a lower power to demonstrate important discernable differences.

**Case control studies** A case control study statistically compares outcomes of a group of patients treated with a new device or procedure to a matched group receiving

no treatment (or a **standard treatment**). Patients in both groups must be well matched on characteristics that are known to influence outcomes associated with treatment for the disease state, such as age or comorbid conditions. Case control studies are often accomplished by searching a large database of patients treated with the standard (or no) device or procedure to find a group of patients that matches the characteristics of those treated with the new device or procedure. A retrospective comparison is then performed to identify which group experienced better outcomes. For example, a new device to treat lumbar disc herniation could be compared to fusion surgery (an accepted technique) by finding patients in a database who have undergone fusion and are matched to patients receiving the new treatment according to age, gender, weight, duration and severity of back discomfort, location of disc herniation, etc. Once a comparable population is identified, researchers could then analyze the medical outcomes of both groups to determine whether the new device or fusion surgery led to more favorable results.

The primary advantages of case control studies are that they are less expensive than randomized studies (see below), can be carried out by smaller teams of researchers, and take less time to complete than prospective studies. The main disadvantage is that the results are not as definitive as prospective, randomized, **controlled** studies and almost always necessitate further research. However, these studies are a valuable step in the development of a technology and can be helpful in revealing both the strengths and limitations of a technology. Case control studies also help innovators understand a potential treatment effect so that large studies can be designed to be successful in meeting statistical and clinical outcomes.

**Prospective, randomized, controlled (blinded) trials**

Prospective, randomized, controlled trials are considered the "gold standard" for medical device testing. They are increasingly required in the US for both approval by the FDA and for reimbursement by CMS (see 5.6 Reimbursement Strategy), which is one reason why the cost and complexity of clinical testing has skyrocketed over time.[4] The term *prospective* refers to the fact that the trial is designed before any devices are tested. The patients are divided into treatment and comparison, or control, groups by a statistically *random* assignment. Interpretation of the results is based on the outcome of the group treated with the new device or procedure, relative to a *control* group that may receive no treatment or treatment with a more established approach. The advantage of prospective, randomized, controlled trials is that they have the greatest statistical **power** to discriminate whether or not the outcome and safety profile of the new technology is, indeed, superior to the control group. The main disadvantage of these kinds of trials is the considerable time and expense required to complete the study compared to the simpler trial structures described above.

In some cases, additional rigor can be added to a randomized, controlled trial if it is possible to **blind** the study participants (patients, physicians, nurses, data analysts) to the device being used. The term "double blind" is used when both the patient and the physician are blind to the treatment. For example, a double blind trial can be performed to assess a bare metal versus a drug-eluting stent if it is not possible for the physician or the patient to tell the difference between the two stents based on appearances or deployment. For the trial, both stents would be provided in nondescript packages with code numbers that would eventually be used to determine which type of stent was placed in which patient. Sometimes in device trials, it is not possible to blind the physician to the treatment (e.g., in the comparison of two implants with a different appearance) and only a single blinded study can be performed.

Before deciding on what study(ies) to conduct, researchers are advised to complete a *thorough* review of available literature for the condition being studied and understand *in detail* what has been studied to date. They should also consider specifying outcomes that are similar to those of previously published studies so that the results can be compared. This is particularly important for observational studies, but is also useful in randomized, controlled studies. Being able to demonstrate how an outcome is significantly better in a trial of a new device compared to the same outcome in a previous trial of an older device can have a significant impact.

Consultation with the regulatory agency, users, and/or payers can help generate the best possible study design, with modifications made as input is gathered.

Innovators are also encouraged to investigate emerging trends in clinical trials focused on finding less expensive ways to generate reliable, informative results. Although randomized trials are still among the most powerful tools available to clinical researchers, there is growing awareness in the scientific community about issues related to their excessive complexity and expense, as well as challenges linked to the time required to recruit study participants and the fact that their results cannot always be generalized to a broader population.[5] In response, registries are attracting increased attention as a mechanism for describing practice patterns and trends, identifying outliers, and detecting safety signals. Researchers are also using registries to assess comparative effectiveness, although they acknowledge that observational findings may not be internally valid owing to the absence of **randomization**.[6]

One response to the trade-offs between randomized trials and registries has been the registry-based randomized trial. A recent example is the Thrombus Aspiration in ST-Elevation Myocardial Infarction (TASTE) trial in Scandinavia.[7] As described in an article in the *New England Journal of Medicine*:[8]

> *The TASTE investigators designed a large-scale trial to answer an important clinical question and carried it out at remarkably low cost by building on the platform of an already-existing high-quality observational registry. With this clever design, which leveraged clinical information that was already being gathered for the registry and for other preexisting databases, the investigators were able to quickly identify potential participants, to enroll thousands of patients in little time to avoid filling out long case-report forms, to obtain accurate follow-up with minimal effort, and to report their findings, all for less than the amount of a typical [individual research grant from the National Institutes of Health]. Their findings may well be broadly generalizable, since they included in the randomization process the majority of all patients treated for ST-segment–elevation myocardial infarction in the study area.*

Although this specific approach will not be applicable to all situations, it is representative of the innovative thinking that can unlock new opportunities in trial design and execution. Another example can be found in the work of the United States' Patient-Centered Outcomes Research Institute (**PCORI**), which is seeking to improve clinical practice through the better implementation of **evidence-based** research. Through its PCORnet program, it is experimenting with models to advance the shift in clinical research from investigator-driven to patient-centered studies.[9]

### *Other trial nomenclature*

As it relates to studies conducted to secure FDA regulatory approval, the term "**pilot**" is used to describe early clinical trials, usually conducted as a registry. The definitive clinical trial conducted for approval (and perhaps reimbursement) is known as a "**pivotal**" trial. "**Post-marketing**" studies refer to trials performed after the commercial approval of the device. These studies are often required as a condition of approval for a PMA device, but also can be used for other purposes as part of a staged clinical strategy. (See online Appendix 5.3.1 for more information about pilot, pivotal, and post-marketing studies and a comparison to trials in the pharmaceutical industry.)

## Basic issues in designing a trial

When designing a specific trial, innovators must consider a number of important factors, including the trial's hypothesis, endpoints, and its statistical power and size.

### *Hypothesis*

The design of a clinical trial starts with a hypothesis, which the study will prove or disprove. Generally, this is in the form of a comparison of the outcomes (endpoints) achieved in patients treated by a new device or procedure relative to the control group. For example, a hypothesis for an ophthalmology trial might be that a new intraocular lens will provide superior visual acuity and an equivalent safety profile to an existing lens.

For the purposes of FDA regulation in the US, an innovator or company might define a hypothesis that the device being studied is equivalent or "non-inferior" to an existing standard; that is, the outcomes are statistically indistinguishable. From a statistical standpoint, equivalence can usually be demonstrated in a much smaller trial than would be required to show superiority. A company might undertake an equivalence trial even if it thinks its device is better than the competition's, because it could save a substantial amount of money and still sell effectively against the competition based on the performance of its device.

*Endpoints*

The efficacy of a new device or procedure is measured in the form of *endpoints*. Endpoints are the prospectively identified and quantifiable parameters that a study is designed to meet. The endpoints relate to the regulatory claim that is being sought for clinical use. Well-designed studies one or more **primary endpoints** which the company, investigators, and regulatory agency agree will be the main criteria on which the device or procedure is evaluated and the one(s) which the study will focus on from a power standpoint (see below). There may be **secondary endpoints**, which are of interest scientifically and clinically, but will generally not lead to a regulatory approval (e.g., endpoints to determine cost-effectiveness for reimbursement). Selection of the proper endpoints for any study is exceedingly important and, is usually a major point of negotiation between the company and the regulatory agency.

To be useful, an endpoint must be measurable and as unambiguous as possible. For instance, even in situations in which the outcome is improved **quality of life** (e.g., a new treatment for tennis elbow), some method of measuring that outcome should be utilized (e.g., a quantitative questionnaire designed to measure the degree of improvement). Another important consideration is that the trial endpoints must be achievable in a reasonable span of time. A new cardiac device may have the potential to prolong life, but the company will not be interested in a trial that takes 40 years to prove this point statistically. In this situation, a **surrogate endpoint** must be selected. For instance, in the cardiac example, the surrogate endpoint might be a measure of the pumping function of the heart and a nuclear medicine measurement of its blood supply – variables which have been shown in previous studies to correlate with survival.

Importantly, the statistical power of an endpoint is maintained only when it is identified prospectively. Post-trial data analysis ("data dredging") may suggest that some unanticipated subgroup of patients seems to gain special benefit from the device. However, to prove this rigorously, it will be necessary to test this endpoint prospectively in a new trial.

Before deciding on the endpoints for a study, the innovator or company that will sponsor the trial should complete a thorough review of available literature for the condition being studied and understand in detail what has been learned to date. Additionally, it will be helpful to select outcomes that are similar to those of previously published studies so that the results can be compared. This is particularly important for observational studies, but is also useful in randomized, controlled studies. Being able to demonstrate how an outcome was significantly better in a trial testing a new device compared to the same outcome in a previous trial of an older device can have a significant impact.

*Statistical power and trial size*

One of the most important issues in trial design is the number of patients to include in the study. A properly designed trial uses a "**power calculation**" to determine how many patients are required in the treatment and control groups to adequately test the hypothesis. This calculation is based on a best guess of the impact of the new therapy on the primary endpoint. For example, suppose a new technology for obesity has been tested in a pilot observational study and has been shown to reduce body mass index (BMI) in the study group by 20 percent. The company and investigators might propose a primary endpoint of 10 percent BMI reduction. This means that if the device truly reduces BMI by 10 percent, the results from the trials will prove that. The clinical trial will then collect data to perform a hypothesis test. The null hypothesis is that there is no difference and the alternative is that there is a 10 percent improvement. The null hypothesis will be rejected if the difference

between the BMI in the control group and treatment group has a **statistical significance** of 5 percent. Because of the randomness in the data, it is possible, especially if the number of patients enrolled is small, that the null hypothesis will not be rejected even if the device has an effect. The statisticians will help determine the sample size such that the chance of erroneously failing to reject the null hypothesis will be small (typically 10 percent). The endpoints and power calculations will be reviewed by the regulatory agency and approved or modified as its experts see fit.

It may be possible to achieve the goals of the power analysis using other forms of randomization besides a 1:1 model. For instance, when the control group will be treated with a relatively well-understood procedure or technology, it may be possible to perform a 2:1 randomization (that is, the group receiving the new therapy will be twice the size of the control group). This approach reduces the size and expense of the trial without negatively affecting the significance of the results. (See online Appendix 5.3.2 for a basic primer on statistical design.)

## Clinical trial planning and operations

Beyond the design of the trial, innovators must address a series of important issues in planning and preparing to launch a trial, as outlined in the sections that follow.

### *Choosing investigators and centers*

An innovator or company, as the sponsor of a clinical trial, will select one or more principal investigator(s) (**PIs**) for a trial based on a number of considerations, including experience in leading trials, track record of publishing trial results, stature in the field, quality of support personnel and – an increasingly important criterion – freedom from financial conflict of interest. The PIs will typically help the company select additional investigators to conduct the trial. These investigators will be chosen based on their technical skill with similar devices or procedures, their ability to enroll patients quickly (generally meaning bigger practices), their prior experience with clinical trials, their reputation among their colleagues, the effectiveness of their research support staff, and their geographic location.

Finding highly productive investigators can be facilitated by searching the literature (looking for contributors who appear on the prior studies that are similar to the one being designed). Polling companies and contract research organizations (**CROs**) that have worked in the specific therapeutic area can also be helpful. However, newcomers (physicians who are new to a particular field) should not be overlooked, as they often can make significant contributions to the trial. Many up-and-coming physicians are hungry to make a mark. Being associated with marquee physicians through a clinical trial can be highly motivating to these new physicians and, as a result, can yield significant enrollment from lesser-known sites.

Typically, all investigators and their institutions involved in a trial will sign a contract with the trial sponsor that specifies their obligations, including accurate recording of data and timely reporting of complications. These agreements also address indemnification and the assignment of ownership rights of new discoveries (IP) made in the course of the study. The investigators and their centers are reimbursed for their costs in conducting the study, which includes their time (and staff time), extra equipment, tests, hospital time, and other expenses. If the investigators are faculty members in a university, the contract is made with the university and an "indirect" charge (typically an additional 25–50 percent) is added to support general university infrastructure. Innovators and companies should expect contracts to take anywhere from 2 to 12 months to finalize, depending on the type of institution with which they are working.

The number of investigators and centers required depends on the size of the trial and the expected rates of enrollment. In practice, enrollment often turns out to be much slower than the investigators believe will be the case. A rough rule of thumb to help manage this risk is for the sponsor to budget for the pace of enrollment to be approximately half as fast as expected and total enrollment from each center to be half as large as projected.

### *Investigational device exemption*

As noted in 4.2 Regulatory Basics, most clinical studies in which there is risk to the patient and in which data will

be used to support a regulatory submission in the US, require an investigational device exemption (**IDE**). An IDE allows a premarket device to be tested in humans such that the necessary safety and effectiveness data can be collected to support the FDA submission. For a PMA, clinical studies supported by an IDE are always required. In contrast, an IDE is only needed to support the small percentage of 510(k) submissions that requires clinical data. An IDE can also be used to cover the clinical evaluation of certain modifications and/or new intended uses of legally marketed devices[10] (e.g., off-label usage).

The purpose of the IDE process is to ensure that researchers "demonstrate that there is reason to believe that the risks to human subjects from the proposed investigation are outweighed by the anticipated benefits to subjects and the importance of the knowledge to be gained, that the investigation is scientifically sound, and that there is reason to believe that the device as proposed for use will be effective."[11] Once approved, an IDE clears a device to be lawfully used in conducting clinical trials without the need to comply with other FDA requirements for devices in commercial distribution. All clinical trials that include investigational devices must have an approved IDE *before* the study is initiated, unless the device is determined to be exempt from IDE requirements.[12]

To obtain an IDE, researchers must complete an IDE submission. As discussed in 5.4 Regulatory Strategy, early communication with the FDA and a pre-IDE meeting can help facilitate more efficient approval through the IDE process, as well as assisting with the development of a study design that supports the desired/necessary endpoints for regulatory approval. The FDA is mandated to respond to every IDE application within 30 days. Though an IDE is rarely approved in the first 30-day period, the FDA must provide the applicant with feedback and/or request additional information within this time frame. Often a series of back-and-forth communications with the agency is required before an application is approved. If, after 30 days, the FDA has not responded to an IDE application, a company is authorized by default to proceed with the study.

During the study, the researchers must maintain compliance with specific IDE requirements which include (but are not limited to):

- Obtaining advance approval from the institutional review boards (**IRBs**) where the study will be conducted, and working with the IRB through the execution of the trial.
- Obtaining **informed consent** from all patients involved in the study.
- Labeling the device for investigational use only.
- Carefully monitoring the study.
- Completing all required records and reports.

In rare circumstances, the FDA allows for investigational devices to be used in patients that are not part of an IDE-approved clinical trial. Such usage is allowed under clearly defined conditions of emergency use, compassionate use, treatment use, or continued access[13] (see online Appendix 5.5.3 for more information).

*Institutional review board approval*

Once an IDE is obtained, researchers must then seek IRB approval before the study is initiated (note that if the study is IDE-exempt, IRB submission is the first step following the design of the trial protocol). It is a federal mandate that each site where a clinical trial will be conducted has an IRB that is responsible for protecting the rights, safety, and welfare of research subjects. The IRB can be developed and managed in-house or contracted from a third-party provider. In either scenario, IRB are regulated by the FDA and their policies and practices are subject to periodic review and certification. An IRB is generally made up of clinicians, nurses, and one or more hospital administrators. Optimally, the IRB will also include a statistical expert, an expert in medical ethics, and one or more "lay" representatives (such as community advocates, clergy members, or a working professional). The IRB is responsible for monitoring complications of the study and, in many cases, also serves as the screening point for issues of conflict of interest on the part of the investigators or their institutions.

The lead **clinical investigator** is responsible for preparing the application to the IRB at each institution where the study will be conducted. This application describes the device, outlines the proposed clinical study and trial endpoints, and includes a sample patient consent form. The IRB formally reviews this

application, often requesting changes as needed, before approving the study. This process usually takes several months to complete. It can require more or less time, depending on how often the members of the IRB meet and how they work together.

It is worth noting that local IRBs often have additional policies and restrictions beyond the general requirements specified by the FDA. IRBs have come under increased scrutiny recently, in part as a result of the 1999 death of a patient enrolled in a gene therapy trial at the University of Pennsylvania. In this case, involving 18-year old Jesse Gelsinger, it was alleged that the IRB did not adequately review the safety of the study and the protections put into place. Furthermore, investigators did not adequately counsel participants on the extent of the risks involved in the study[14] and were not following all of the federal rules requiring them to report unexpected adverse events associated with the gene therapy trials.[15] The Gelsinger case, in conjunction with other events, served as a catalyst for IRB reform and the improved protection of human research subjects. In June 2000, the Office for Protection from Research Risks (OPRR) was officially renamed the Office for Human Research Protections (**OHRP**) and moved from the National Institutes of Health (NIH) to the Department of Health and Human Services or **HHS** (which also oversees the FDA). The move was intended to increase both the visibility and accountability of human research protections, as monitored by the federal system.[16] To carry out this mission, the OHRP has established formal agreements ("assurances") with nearly 10,000 universities, hospitals, and other research institutions in the US and abroad to comply with the regulations pertaining to human subject protections.[17]

Because each IRB maintains its own governance, trial sponsors may have an inconsistent experience from institution to institution. Sponsors and investigators should be prepared to modify their **clinical protocols** (and especially the informed consent document) to meet the requirements of each IRB. It is the sponsor's responsibility to ensure proper document control for each location, a practice that can present complex control/management issues for trials that utilize multiple sites.

It is also important to note that many IRBs charge for their services (i.e., initial review and approval of the study, as well as ongoing reviews). An initial review can cost anywhere from $2,000 to $4,000, while ongoing reviews may range from $1,000 to $2,000 every 6 to 12 months, with these fees paid for by the sponsor.

*Patient enrollment*

Patients are screened for studies by the investigator and his/her staff. In the modern era of careful trial design, IRB review, and patient advocacy, the ability of researchers to enroll subjects has become the rate-limiting resource in clinical research.[18] Despite this challenge, innovators and companies must carefully adhere to all guidelines and requirements for enrolling their trials (see Figure 5.3.4).

There is no doubt that patients are increasingly cautious about agreeing to participate in trials of new devices and drugs. A recent article summed up the patient's perspective about participating in a cardiac defibrillator trial this way: "Would you sign up for an experimental heart device trial, where there's a


FIGURE 5.3.4
In today's environment, innovators are cautioned not to take chances in performing human research.[19]

50 percent chance your device will be inactive ('control group'), and there's an FDA-approved device already on the market?"[20] For those involved in sponsoring and conducting clinical trials, it is important to keep in mind a key fact: volunteering for a clinical study is an act of generosity and public service on the part of the patients and their families. As a result, study participants should receive all the respect and gratitude they deserve.

The process of enrolling patients into a study must be meticulous and is often highly time-consuming. Subjects must be evaluated carefully and thoroughly to determine if their conditions and health profiles match the targeted audience for the device. This is accomplished through detailed screening using:[21]

- **Inclusion criteria** – Characteristics or indications that subjects must have in order to participate in the clinical trial. For example, if a new spinal disc is being tested, participants might be required to demonstrate a specific site of disc degeneration in the back to be included in the study.
- **Exclusion criteria** – Characteristics or contraindications that eliminate subjects from participating in a clinical study. For example, individuals who have had fusion surgery or advanced spinal arthritis might be excluded because their spines already show significant differences from those that a device is intended to treat.

Meticulous patient screening involves multiple participants in the care continuum. First, patients must be correctly diagnosed. Then, their physicians must be familiar with the clinical studies available for which the patients might qualify. Researchers often impose other requirements and testing procedures on patients to ensure that they fit the trial criteria. At the same time, patients may seek counseling from another healthcare professional, particularly if they are dealing with stressful or life-changing news regarding the illness.

It is worth keeping in mind that patients can benefit from trial participation in several ways. The new technology or procedure may indeed represent a substantial improvement in care. Even if allocated to the control group, the patient may benefit from the increased level of medical attention provided to participants in the trial, including additional tests and provider visits. Patients also appreciate the chance to learn more about their condition by participating in a study. Some studies will reimburse patients for their participation in the trial, particularly if there is a requirement for the patients to return for further evaluation or testing. Finally, and perhaps most importantly, many patients are genuinely motivated by a desire to serve others. Having suffered themselves, they are inspired to do what they can to reduce or eliminate the medical problem for subsequent patients.

*Informed consent and patient protection*

Before entering a study, patients must provide written *informed consent*. In practice, this means that someone (generally not the physician performing the procedure) reviews the IRB-approved consent form with the patient, explains the risks and benefits of the study, answers any questions, and obtains the patient or guardian's signature on form. The consent form provides the opportunity for the patient to withdraw at any point in the study and identifies a third party, who can be contacted if there are perceived irregularities or other issues with the trial.

Standards governing the protection of human research subjects, including mandatory informed consent, arose from several shameful experiments conducted in the early part of the twentieth century (most notably in Nazi Germany and in Tuskegee, Alabama). The standard of informed consent emerged in the 1940s as the field of clinical research became codified and well established. Today, requirements for informed consent in research involving human subjects exist in every country, as defined by international standards.

Because new investigational devices have not, by definition, been tested previously in humans, a certain level of risk exists for the subjects involved in any clinical trial. As the level of device invasiveness and procedure complexity increases, so does the level of risk. According to the FDA, "Although efforts are made to control risks to clinical trial participants, some risk may be unavoidable because of the uncertainty inherent in clinical research involving new medical products. It's important, therefore, that people make their decision to participate in a clinical trial only after they have a full understanding of the entire process and the risks that may be involved."[22]

This philosophy is at the heart of the FDA's policy for informed consent, which states:[23]

> *No investigator may involve a human being as a subject in research covered by [FDA] regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.*

*Data entry and monitoring*

In many medical device trials, the time at which the device is used represents a critical point in the study where intensive data collection is typically performed. Generally, this is accomplished by a study nurse or other trained expert who collects all of the pertinent information about the encounter. The primary data can be kept carefully in files or notebooks (see Figure 5.3.5) or more recently documented by electronic data capture. It is the responsibility of the sponsor to regularly monitor the primary data to ensure quality and to evaluate adherence of the investigators to the protocol. Protocol violations must be carefully documented and tracked. Investigators are often counseled about their continued involvement in the trial if there are problems with the quality of the data or compliance with the protocol. This entire process is also subject to auditing by regulatory agencies.

*Core laboratories*

Certain endpoints of a clinical study may best be analyzed in a special **core laboratory**, staffed by clinical scientists with specialized equipment and expertise to make the quantitative measurements required. These core labs also add a level of consistency and objectivity to data analysis in that they are independent of the investigators and sponsor. Core laboratories may be in universities or private clinical research organizations. For example, clinical trials of coronary stents routinely use core angiographic laboratories, where


FIGURE 5.3.5
Clinical research nurses and coordinators must keep detailed records on every enrolled patient (courtesy of Todd Brinton).

radiographic images of the arteries (angiograms) before and after stent placement are carefully measured. Core laboratories typically charge on a per-patient basis and are subject to audit by the FDA.

*Clinical events committee*

Studies with the potential to harm patients must include mechanisms for evaluating clinical events. Clinical events are clinical signs or symptoms that occur during the course of the study. Monitoring of these events is often accomplished through an independent review committee. The clinical event committee (CEC) usually comprises clinicians and statisticians who are charged with independently adjudicating clinical events and reporting the results to both investigators and the study sponsor. Clinical events are typically screened as adverse events (AEs) or serious adverse events (SAEs). The committee must determine if its members believe the event is not related, possibly related, probably related, or related to the procedure or the technology. For example, consider a patient who receives a new cardiac pacemaker but then experiences pain for an extended period following the procedure and ultimately develops an infection of the implant several weeks after the placement. The committee would review the hospital records and reports, including all tests and might deem the pain an AE probably related to the procedure and device. Further it may also determine that the infection is an SAE related to the procedure, but only possibly related to the technology since the infection was most likely a result of contamination of the surgical site and not the device itself. These results are important data points that impact the safety endpoints of a trial. Members of the CEC are compensated by the sponsor but cannot have further financial ties to the company. The reports of the CEC must be available for auditing by the regulatory agencies.

*Data safety and monitoring board*

Sizable trials will generally have an independent data safety and monitoring board (**DSMB**) to review the preliminary results at prespecified time points during the trial in order to ensure that patients are not being inadvertently harmed by the study. The DSMB may decide that the initial trial results are within the range of expected outcomes and allow the trial to continue; it may terminate the trial based on unexpectedly bad outcomes in the treatment group; or it may terminate early based on unexpectedly good results (when it is no longer ethical to continue the control treatment).

## Clinical trial management

Once the trial has been launched, innovators must next address a number of ongoing management issues to ensure the timely and effective completion of the trial.

*Research site staff*

The resources required at each center to perform the high-quality research necessary for a randomized, controlled trial are formidable. In addition to the resources needed to initiate and manage a clinical trial program at the site (including physicians, facilities, and equipment), the study center must devote research nurses to each study. Research nurses play an instrumental role at all phases of the trial, including general study management, IRB process management, and accurate completion of case report forms. It is the sponsor's responsibility to make sure each clinical site has the necessary resources in place to fulfill the demands set forward in the protocol.

*Sponsor personnel*

Most sponsors will have at least one or two in-house employees managing a clinical trial, if not an entire team (depending on the level of control and support the company determines to be appropriate). Different models commonly adopted by trial sponsors include the following:

- Companies may engage a CRO to manage the on-site elements of the study, as well as data management. A CRO typically provides the infrastructure required to recruit, qualify, and audit sites. A CRO is particularly beneficial when the scope of the trial is large and the CRO has experience in the type of study being conducted. Also, because of the transient nature of clinical trials, it may not make sense for a company to hire an entire staff of full-time

researchers who will not have roles when the trial ends.
- Alternatively, some companies prefer to maintain tight control over a clinical study by managing it in-house. In these cases, certain elements of a trial still may be outsourced [some CROs offer "a la carte" services, such as monitoring only, data management, or regulatory (IRB, IDE, etc.) responsibility], but the overall management of the trial is still performed by the internal team.

The sponsor, or its CRO, has responsibility for monitoring the progress of the trial, compliance with the protocol, and various other requirements. When using a CRO, the external organization should be carefully managed. All contracts also should be explicit with respect to expectations and deliverables. Outsourcing can be risky since the contractor does not have as much at stake as the sponsor. On the other hand, CROs have vast experience and expertise that can be valuable to young, start-up companies. Close, proactive management of any external partners can help minimize this element of risk while capitalizing on its benefits.

*Data management*

Data management is perhaps one of the most important elements of a clinical trial. However, this factor often is overlooked until the data already have been captured. Traditionally, paper forms are completed for each patient at each visit. These data forms must then be entered into a database to track progress of the endpoints of the study. Increasingly, web-based data capture is being used, which minimizes the back and forth of case report forms through fax or email. Another advantage of these web-based systems is that they can be designed to accept only data that fall within expected limits (i.e., data that make sense), prompting the person entering the data to recheck the values that violate defined expectations.

## Clinical trial costs

As noted, the cost of medical device clinical trials can account for a significant portion of a start-up's total budget on the way to market. Based on the purpose and complexity of the study, the costs for medical device clinical trials can range from hundreds of thousands to tens of millions of dollars. Study costs are driven by:

- The cost of the device(s) being used in the trial.
- The cost of performing the procedure, including physician costs and hospitalizations, if needed.
- The costs of follow-up clinical visits and/or tests to evaluate the safety and efficacy of the medical device.
- The cost of paying investigators and institution study coordinators to perform the clinical studies.
- The cost of conducting the trial, including training, monitoring, and data management.
- Patient recruitment costs, including advertising and potential payment to patients.
- In-house management and personnel costs.
- The cost of trial support and other resources provided by CROs.
- IRB costs.
- Consulting expenses for data safety monitoring boards, physician advisory boards, and core laboratories to independently evaluate trial results.

Clinical trial expenses may range from as little as $2,000 per patient (e.g., for a non-implantable device with a short follow-up period) to as much as $100,000 on a per patient basis (e.g., for an implantable or therapeutic device with a lengthy follow-up period). Investors will show a greater or lesser willingness to fund a device with high anticipated clinical expenses based on factors such as the size of the total market opportunity. As the Respira team (featured earlier) learned with its low-cost asthma spacer targeted at underserved patients in developing countries, raising money to conduct even inexpensive trials can be difficult without a strong commercial opportunity for selling the device. Companies with devices that require trials at the higher end of this range are often expected to have a device with "blockbuster" market potential.

Within start-up medical device companies that expect significant clinical trial program costs driven by a PMA regulatory pathway in the US, financing rounds are often coordinated with clinical trial milestones. It is not unusual for series B or C (early to mid-stage) financing to correspond to milestones for first-in-human or pilot studies. Series C to E (mid to late-stage) financing tends

to correspond to milestones related to pivotal trials (see 6.1 Operating Plan and Financial Model and 6.3 Funding Approaches). The close interplay between financing and clinical trial milestones underscores the importance of staging clinical studies and gathering results to build sequential value to a company which can, in turn, justify subsequent rounds of funding. It is also indicative of the significant financial burden that is associated with a clinical program. To efficiently manage this sizable expense, as well as the other important issues related to clinical studies, careful strategic planning is essential.

## Location of clinical studies

Researchers also must consider whether or not to conduct clinical trials within the US or outside the US, based on their objectives, particularly with regard to where device approval is ultimately desired. The most common reasons that studies outside the US are favored, particularly for first-in-human testing, are for increased patient access, quicker enrollment, and reduced cost. Locations such as Austalia, Central and Eastern Europe, and Central and Latin America have developed burgeoning ecosystems and a deep bench of qualified investigators to efficiently and cost-effectively support the clinical trials of medtech companies from around the world. Accordingly, a sizable percentage of clinical device testing has shifted overseas. For example, one literature review found that the number of countries serving as trial sites outside the United States more than doubled from 1995 to 2005, while the proportion of trials conducted in the United States and Western Europe decreased.[24]

Another reason that innovators have been encouraged to globalize their clinical strategies is because initiating a US trial has historically been more difficult and time-consuming than launching a study in another country. For instance, a survey of more than 200 medical device companies found that the average time required to obtain an IDE was nearly 14 months. Respondents reported that many delays were linked to disagreements with the FDA regarding the definition of primary efficacy endpoints (27 percent), the definition of primary safety endpoints (15 percent), and other factors such as the use of historical controls (8 percent), size of the trial (12 percent), statistical techniques (6 percent), and/or the need for randomization (5 percent). Once an IDE was obtained, it took these companies an average of 21 months to conduct a pivotal trial that was designed to satisfy FDA's requirements, with no assurance of the adequacy of the FDA-mandated study design.[25] Such delays are one factor that can add significant time and cost to conducting trials in the US. Another is the tendency in the US to demand larger and more extensive clinical trials than regulatory agencies in locations such as the European Union. As the author of one article described, "The European approach places more responsibility on physicians and their clinical judgment rather than on government officials who may have little appreciation of or experience with the exigencies of the clinical circumstance."[26]

That said, regulatory and study monitoring protocols for trials outside the US are gradually becoming more stringent, particularly as developing countries adopt international guidelines on the performance of clinical trials. For example, India recently passed a new policy meant to protect patients who participate in clinical research studies performed within the country. The intent of the new rules has been praised, but some observers have raised concerns about the burden the policy creates for companies and researchers.[27] As described in 4.2 Regulatory Basics, the long-term effects of the policy remain to be seen, although the expectations is that it will significantly reduce the number of trials conducted in India.[28] Nonetheless, depending on the disease state or condition being studied, patients can still be enrolled more quickly in overseas locations where the patient volume is simply higher.

When considering a clinical strategy that involves trials in overseas locations, it is important for companies that eventually intend to target the US market to understand that the FDA may not consider the patient population treated overseas to be equivalent to a population in the US. In order for these clinical data to be relevant for the US regulatory process, the patient population must be comparable (ethnically, as well as in terms of treatment regimens) to that of the US population. As a result, careful guidance should be pursued prior to the initiation of a trial to ensure that data collected outside the US will be accepted by the FDA if that is an assumption within the company's clinical strategy.

Clinical trials performed for FDA PMA regulatory approval are predominantly performed in the US. Companies may include globally dispersed sites in large pivotal studies to increase enrollment and gain footholds into important markets where they intend to bell the device. However, when the US is the ultimate target market, the majority of clinical sites should be based there. The FDA often looks favorably upon data from studies conducted outside the US as a precursor to an IDE to validate initial safety testing of the device. As a result, these studies can be a useful strategy in this regard for companies preparing to conduct pivotal trials in the US.

**Working Example**

An overview of good clinical practices for conducting clinical trials

When conducting a trial in the US under an IDE, the investigators, sponsors, IRBs, and the devices themselves are all subject to Good Clinical Practices (**GCP**) regulations. These guidelines are analogous to FDA's GLP guidelines for the execution of preclinical studies. They outline specific standards for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials to provide assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. Resources for learning more about GCP regulations can be found in the Getting Started section.

Importantly, IDE-exempt trials are subject to their own regulations (outlined in FDA's exemption regulation), which are not quite as robust as GCP requirements. However, it is worth noting that even exempt trials should comply, at a minimum, with all GCP requirements regarding the protection of human subjects if their credibility is to be maintained.

## A note on conflicts of interest in clinical trials

Conflicts of interest in the context of clinical trials refer to a situation where an individual or group has potentially competing interests in the outcome of the trial – for example, wanting results that benefit the patients in the trial but also seeking outcomes that benefit the company that has worked hard to develop the new technology. There are different kinds of competing incentives for different **stakeholders** in the clinical trial process. For instance, the lead physicians may be strongly motivated to have positive study results that can be published in an important medical journal. But, without question, the conflicts that receive the most scrutiny are those related to financial ties to the success of the product.

Financial conflicts of interest are essentially an unavoidable part of the testing of new medical technologies. Clinical trials of new technologies are so expensive that governmental health agencies like the NIH or the FDA can only sponsor a tiny fraction of the trials that need to be conducted. Companies are expected to take on the financial burden of the trials. In doing so, they automatically assume a conflict of interest in the process. As a result, sufficient regulatory checks and balances must be maintained to ensure that these conflicts do not significantly distort trial data.

It is important to understand that conflicts of interest occur at all organizational levels. Any individuals who participate in the trial could have a potential conflict if they stand to benefit financially (or by reputation, publications, etc.) from the outcomes. Their institutions also may have a conflict of interest. For example, a university may receive **royalties** on a new technology that one of its faculty members has invented. In the current climate, many universities would opt not to participate in the clinical testing of the device because of this financial conflict of interest. The national press has recently highlighted a number of examples of physicians and medical centers that have received questionable payments from pharmaceutical and device companies.

A special situation arises when physicians are involved in the invention and early development of a device and, as a result, play an integral role in the early studies. Through this involvement, the clinician/inventor obtains in-depth, first-hand knowledge of the device's performance and its failure modes. Given this experience, it may be most ethical from the standpoint of patient safety for these physicians to perform the first clinical studies. However, because these clinician/inventors often have

leadership and/or equity positions in the company developing the device, careful steps must be taken to mitigate and manage conflicts of interest. This situation is recognized in the Association of American Medical Colleges (AAMC) guidelines on conflicts of interest, which allow the conflicted surgeon/clinician with substantial preclinical experience to perform the first-in-human studies, but recommend that these individuals not serve as principal investigators in any definitive, multi-center trials.[29] In addition to processes put in place by the various IRBs at the clinical facilities where the studies are conducted, the FDA's IDE process requires disclosure by any investigators with a significant equity or consulting stake in a company. Investigators are not barred from participating in studies involving their devices, but the nature of the relationship with the company must be disclosed to the FDA, the IRB, and the subjects in the study.

## Tips for designing and managing successful clinical trials

A few final words of wisdom can be helpful for innovators and companies as they prepare to engage in clinical trials:[30]

- Collect data early on enrollment patterns from the different centers. This exercise provides a realistic view of the speed of the overall trial and can help to ensure that each clinical research site is screening all patients and is giving the study top priority.
- Statistics only summarize the data. Examine the real data directly to look for early indicators and issues.
- Beware of drawing inferences from small samples over large populations. Design the pivotal trial keeping in mind that results from the pilot might be overly optimistic. Review all data that have been published to date as a "sanity check" of what has been achieved in the field so far.
- Resist the temptation to develop an overly ambitious study design. Review the company strategy and plan a study that seeks to answer important questions reflected in the study endpoints.

Selecting endpoints for trials is a significant challenge, and clinical experts often have different opinions about what endpoints are most appropriate. However, the company and its clinical investigators and advisors must be aligned in their goals for studying a technology. The classic story about the company Devices for Vascular Intervention highlights how interactions between the company, scientific advisory board, and principal investigators can be challenging when designing a clinical trial. It also underscores the importance of thinking about each trial as one part of an overarching clinical strategy.

## FROM THE FIELD DEVICES FOR VASCULAR INTERVENTION

### The overall importance of clinical strategy and trial design on business success

In the mid-1980s, John Simpson pioneered the concept of directional coronary atherectomy (DCA). The DCA procedure used a device called an AtheroCath® to cut, capture, and remove plaque from the coronary arteries. The need for the device was created by the ongoing desire in the field for a less invasive, more cost-effective solution to removing obstructive atherosclerotic lesions than cardiac artery bypass grafting (CABG), as well as the perceived failure of percutaneous transluminal coronary angioplasty (PTCA) to yield a durable result for all patients.[31] Simpson believed that the clean removal of plaque through atherectomy would render a larger and less traumatized lumen and, therefore, less restenosis.[32] He founded Devices for Vascular Intervention (DVI) as a mechanism for developing and commercializing this new approach (see Figure 5.3.6).

Allan Will joined DVI in 1986 as vice president of marketing and sales and became the company's CEO in 1987. "At that point in time, most of our work was focused on what we would need in order to translate our success in peripheral vessels to the coronaries and get

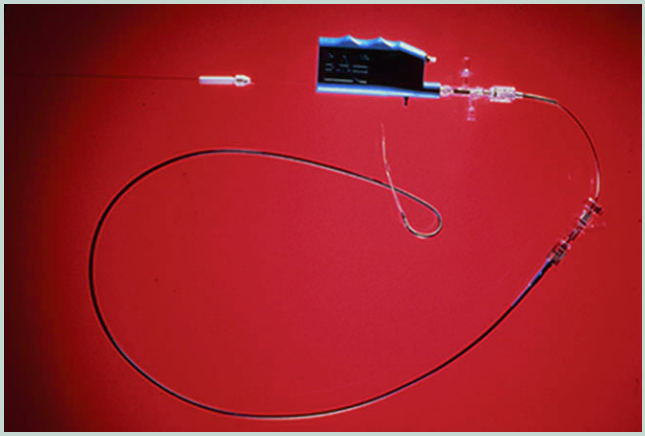

FIGURE 5.3.6
The DVI AtheroCath (courtesy of Allan Will).

the coronary product approved by the FDA," Will recalled. "We knew that eventually we would be involved in a large-scale clinical study." Between 1988 and the time of the company's advisory panel meeting in 1990, clinical testing of the AtheroCath in 873 patients was performed at twelve US hospitals. The value of DCA was assessed by means of a large patient registry that catalogued acute and late clinical outcomes and then compared them to a historical control. "Ultimately, our final PMA registry data included roughly 2,000 patients," Will said. "These data were compared against generally accepted angioplasty results. During this initial clinical study, we used the commonly accepted threshold for a significant stenosis – greater than 50 percent residual stenosis – as our success endpoint." Data from the study indicated that DCA achieved comparable or better results than those achieved by balloon angioplasty and pointed to a lower incidence of serious coronary dissection and abrupt occlusion after DCA.[33] DVI received FDA approval of its device in September 1990 based on the outcome of this study. AtheroCath use grew quickly after its US commercial launch. "Sales grew from approximately $10 million in the year of FDA approval, to $41 million, then $60 million, and finally $84 million in our third full year," Will noted.

In the meantime, however, DVI was acquired by Eli Lilly in 1989. "As part of that **acquisition**," explained Will, "Lilly wanted to include an **earn-out**, so that the value they ultimately paid would be based upon actual versus a speculated value. And they originally proposed that a very significant amount of the earn-out – I believe it was around $25 million – should be based on the results of a prospective, randomized clinical study demonstrating at least a 50 percent reduction in restenosis compared to PTCA. At the time, we didn't even know the full results of our approval study, let alone how the device would perform in a hypothetical, prospective, randomized clinical study." Moreover, these kinds of studies, while common in pharmaceuticals, were relatively new in the medical device industry. According to Will, "I believe this was the first seriously conducted prospective randomized clinical study of a medical device in the field of interventional cardiology."

Will and team "pushed back" on the proposal from Lilly's management. "There was just so much we needed to learn about how to best use this device before we launched a definitive trial," he said. DVI was ultimately able to negotiate the amount of the earn-out that was linked to the clinical study down to $5 million, but Lilly management insisted that the company conduct it.

In an effort to better understand the procedure and thereby produce the most positive results possible, the DVI team intentionally sought to delay the trial until late in the earn-out period. "We hoped to avoid conducting the study until we learned enough to know how best to use the device," said Will. "We needed answers to questions like how much plaque should you remove, do certain lesions respond differently to atherectomy than other lesions, and do certain vessels respond better than other vessels?" For this reason, DVI waited until 1991 to launch what would become known as the CAVEAT trial.

Will and his clinical staff also worked carefully to propose a study design. "We had become convinced that in order to get an optimal atherectomy result, you needed to remove enough plaque to achieve less than 20 percent residual stenosis. However, when we proposed that as a technical endpoint for a successful atherectomy and as a guideline for conducting the atherectomies in the study, a couple of very vocal investigators argued back that

requiring clinicians to reach less than 20 percent residual stenosis would **bias** the study toward atherectomy. They told us that if we set that endpoint, it would be the equivalent of saying we're only going to measure the successful atherectomies against all angioplasties. Our argument was that the endpoint for a successful angioplasty was quite well known, because angioplasty procedures had been well proven and accepted for quite some time. All that we were doing was establishing a similar standard for a technique that wasn't yet as widely understood in terms of what the clinical endpoint was."

The need for a clearly defined endpoint was driven, in part, by the fact that DCA was a directional procedure, whereas angioplasty was concentric. When an angioplasty balloon was inflated, "it acted circumferentially on the vessel," explained Will. "With DCA, it was relatively easy to obtain a great angiographic result without performing a complete circumferential atherectomy." To adequately assess a DCA endpoint, the vessels had to be evaluated from multiple angiographic views to ensure completion of the procedure. "Otherwise, the physician might think he or she got a great result even though, when looking axially down the vessel, it had only been atherectomized at 12 o'clock and 6 o'clock, and the result had been assessed by looking at the 'wrong' cross-sectional view."

DVI argued its case aggressively, "But unfortunately, we had selected a principal investigator for the trial who was, if anything, going overboard to ensure that he wasn't favoring atherectomy or the corporation. So any hint in his mind of bias needed to be removed. In the end, that was one of the components to our undoing. We lost that argument, because we had effectively given up control over trial design to the investigator group," Will said. Instead of being able to define an endpoint of less than 20 percent residual stenosis for atherectomy, DVI had to adopt the clinically accepted endpoint at the time for significant stenosis, which was greater than 50 percent. "If you achieved less than 50 percent stenosis, you'd completed a successful procedure as measured by CAVEAT," Will recalled. "We were allowed to 'encourage' clinicians to achieve less than 20 percent, but we were not allowed to require that as a technical endpoint for success."

DVI's troubles continued when its principal investigator initially refused to share the results of the trial with the company in advance of the 1993 American Heart Association meeting where the data were scheduled to be released. "The chairperson of our clinical trial was determined to maintain control over the clinical study until he released the data. We told him, 'We have an obligation to the patients and the clinicians who use our product to understand what the data is and answer questions. When a clinician comes up to us at our booth, what do we say?'" Ultimately, the DVI team secured the data and was able to quickly prepare for its release. But, said Will, "It wasn't pretty because we had not been able to fully analyze the data prior to its release by our PI."

To make matters worse, the results of the CAVEAT trial failed to show any significant improvement in early or late clinical and angiographic outcomes with DCA.[34] Interestingly, according to an editorial in the *Journal of American College of Cardiology*, "The surprise results of CAVEAT led some investigators to question the conduct of the trial. The CAVEAT was a multi-center study with significant variation in operator experience and skills. The failure of DCA to reduce restenosis could not be reconciled with experience at several of the premier DCA centers. A popular theory arose that DCA fared poorly in CAVEAT because the procedure was not performed optimally in all collaborating centers."[35] Two additional studies (BOAT and OARS) were subsequently completed at hospitals with a strong commitment to DCA as a procedure, as well as substantial experience with the technique. In these trials, aggressive atherectomy, usually combined with adjunct balloon angioplasty, led to significant reductions in restenosis rates when compared to balloon angioplasty alone. However, for many, these results were described as being "too little too late."[36]

Reflecting on the CAVEAT trial results, Will acknowledged that "it threw a damper on the business." However, he continued, "What had a much greater impact on the business was that stents were coming on

the scene. The major shortcoming in stenting at that time was recognized to be acute thrombosis. Right around then, Dr. Antonio Colombo had discovered that acute thrombosis post-stenting was caused by an incomplete expansion of the stent. So clinicians began to think, 'Oh, now I can place a stent and not have the acute thrombosis problems that we've been experiencing, and the procedure takes me no longer than an angioplasty would. And maybe I get as good results as an atherectomy, but atherectomy's a lot harder work.' [The average atherectomy took roughly twice as long.] So, it's hard to assess the specific impact that CAVEAT had. Clearly it was negative, and it positioned us to be vulnerable to this finding that came out on stenting. If we had definitively proven in that study that we lowered restenosis . . . perhaps people would have required stenting to have prospective, randomized results before they abandoned atherectomy and ran to stenting. Instead, stenting began to take off even before the release of their prospective randomized clinical studies."

When asked what advice he would offer to entrepreneurs and companies planning clinical trials, Will had this to share: "First, look at trials as incremental building blocks. Don't consider any single trial as the be-all and end-all. Think carefully and strategically about what you need to show in the first study and what you should prove in subsequent studies. Recognize that you're going to learn how the device should be used or optimized and build that into your clinical trial strategy. These days, unfortunately, companies are required by the FDA to prove acceptability in a prospective, randomized study right out of the blocks, with their first large-scale clinical trial. Do what you need to do for the approval study, but don't overreach. Second, be aware that, in order to get paid for these devices, you need to build reimbursement endpoints into your approval study. Third, always opt for likelihood of success and speed of enrollment in your clinical study design. And finally, to as great an extent as possible, maintain control over the design and conduct of your clinical trial while not giving up objectivity. You need to be fair, you need to be honest, and you need to do good science, but it's still valuable to maintain control over the design and conduct of the clinical study."

Will also commented that, "A whole lot of ground has been plowed between when we began the CAVEAT study and today. There's now more than 15 years of experience in the device industry conducting prospective randomized clinical studies. As such, it's a much more accepted practice and there is a raft of principal investigators to choose from – good, bad, and in between. Carefully choosing the right principal investigator is of critical importance . . . one who believes in the potential of the technology, who will conduct a quality, expeditious trial, and who has no agenda other than to fairly and effectively evaluate the technology considering its stage of development." Will also encouraged entrepreneurs to work with experienced consultants in the field and the FDA to design studies that are objective and likely to lead to clearly defined, positive results.

A second story about a company called Emphasys Medical further underscores the challenges of gaining consensus around trial design and execution. In addition, it highlights the fact that the development of a clinical strategy for a new "white space" technology can be a major challenge. Although there are a number of business advantages of being the first to bring a new product forward in a clinical area, one of the disadvantages can be that no roadmap for clinical development exists. When working in clinical fields where previous technologies have been designed and implemented, innovators have access to guidance concerning knowledge of the disease, the heterogeneity of the patient population, effective animal models, and endpoints for study design. By assessing the clinical strategies of other companies working in the space, teams can save tremendous time, effort, and expense. Where this guidance does not exist, defining a clinical strategy can be characterized by

greater than average uncertainty and risk. Seeking input and collaboration from clinical experts, investigators, trialists, statisticians, and regulators can help. But the demands of defining, executing, and funding a clinical strategy that addresses the needs of these many stakeholders can be difficult.

## FROM THE FIELD EMPHASYS MEDICAL

### Navigating complex clinical and regulatory challenges on the path to market – part 1

As described in 2.2 Existing Solutions, Emphasys Medical was launched by medtech **incubator** The Foundry to provide better solutions for patients with advanced emphysema.[37] Emphysema is a form of chronic obstructive pulmonary disease (COPD) in which the alveoli, the tiny spherical air sacs in the lungs, are gradually destroyed. The damaged clusters of alveoli degrade into large, irregular pockets of non-functional lung tissue, reducing the surface area of the lungs available for oxygen/carbon dioxide exchange. In addition, air becomes trapped in these pockets, preventing complete exhalation and crowding the functioning portions of the lung. As a result, patients suffering from the disease must work harder and harder to take in adequate oxygen and feel perpetually short of breath.

Emphysema is irreversible, and there are few treatment options. The **standard of care** is medical management, including the use of oral and inhaled bronchodilators and supplemental oxygen to ease symptoms. For patients with severe emphysema, another option may be lung volume reduction surgery (LVRS), in which the most diseased portions of the lung are surgically removed so the remaining healthy tissue has more room to function. However, because the procedure is highly invasive (requiring the opening of the chest) and the eligible patient population is fragile, LVRS is considered high risk and has limited usage. The only other surgical option is lung transplantation, a last resort that is constrained by a critical shortage of donor organs.

The Emphasys Medical technology was designed to ease breathing in the same way as LVRS but without surgery. The concept was that tiny one-way valves, placed in the major airways leading to the most diseased portions of the lungs, would prevent air from entering the diseased segments but allow air to escape. The team hypothesized that this would cause the diseased portions of the lung to collapse (called atelectasis), creating more space for the healthier parts of the lung to function and making it easier for the patient to breathe. Emphasys demonstrated the technical feasibility of the approach by placing one-way valves into the bronchial passages of sheep. The valves created immediate and total collapse of the treated lobes.

Encouraged by these results, the company developed a novel one-way valve that could be placed through the airways over a guidewire (the same way a stent is placed within a blood vessel – see Figure 5.3.7). The procedure was non-surgical and completely reversible. Led by CEO John McCutcheon, the team completed early **bench testing** then moved into chronic animal studies, using sheep to study the delivery of the device, deployment of the valve, mechanical success, biocompatibility, and safety.

Based on the positive results of its animal studies, Emphasys filed an application with the FDA for 510(k) clearance of the device. “We used a matrix argument with tracheobronchial stents and some surgical products to establish substantial equivalence,” said McCutcheon. “Tracheobronchial stents, one of the few pulmonary devices on the market, were 510(k) cleared, so we thought that this might be a viable approach.” The company’s submission was reviewed by the Plastics and Reconstructive Surgery branch of the FDA’s Center for Devices and Radiological Health (CDRH) because that was where tracheobronchial stents had been assigned. “We expected that the FDA might come back and

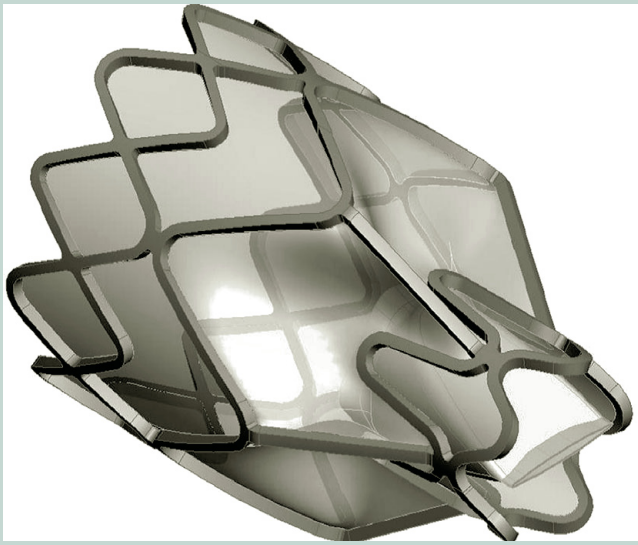

FIGURE 5.3.7
A representation of the Emphasys Endobronchial Valve (courtesy of Emphasys).

require a clinical trial to back up the submission, which we would have done anyway prior to commercialization," said The Foundry partner Hank Plain. "But, they said, 'No, this is definitely a PMA.'"

Knowing that clinical data would be paramount to its success in navigating the PMA pathway, Emphasys considered its next move. Because there was no animal model that replicated human lung anatomy or human emphysema, the team could not measure efficacy through additional preclinical tests. "You can only learn so much on animals," said McCutcheon. "The real learning starts when you get to human clinicals." The team decided to transition into human pilot tests in order to validate the feasibility of the procedure and, more specifically, the safety and effectiveness of the device in humans. Importantly, Emphasys also hoped to learn from the pilot studies which patients were most likely to benefit from the intervention. Emphysema is a complex disease state in that the areas of destroyed tissue can be localized to certain lobes[38] or parts of the lung (heterogeneous), or spread more widely and evenly throughout the lungs (homogeneous). Additionally, the company would study which treatment approach was most effective since the valves could be placed unilaterally (on only one side of the lungs) or bilaterally (both sides), and could include one or more complete lung lobes and/or partial lung lobes. By testing different patient characteristics and treatment approaches during the pilot studies, Emphasys intended to gather enough information to guide the design of the pivotal trial, which the FDA would review as part of the company's PMA submission.

The first ten patients treated with the Emphasys device were in Melbourne, Australia. All had severe heterogeneous emphysema and received bilateral placement of the valves, which, for the purposes of the study, meant that Emphasys treated the right upper lobe without treating the right middle lobe, and treated part of the left upper lobe without treating the lingula. However, none experienced the desired outcome, atelectasis. "We quickly learned that 70-year-old patients with emphysema are very different than juvenile sheep. Their lungs are a mess, and they're much weaker overall. So we didn't see the same kind of dramatic results," said Hanson Gifford, another partner at The Foundry.

Additional pilot studies proved challenging on a number of other fronts. Enrollment was slower than anticipated, as many pulmonologists used to medically managing their patients were reluctant to try an interventional procedure. This unexpected hurdle led to a broad geographic dispersion of trial sites, as well as a wide range of patients in terms of the characteristics of their disease. As a further complication, the team discovered that the valves were leaking in a way that had not been observed in the sheep. Emphasys engineers modified the design and continued gathering data.

Following the introduction of the modified device, the team began to see some encouraging clinical success. However, as more data from the pilots became available, the company observed significant variability in success rates among the sites without any clear reason for the difference. Reflecting more than the redesign of the valve, the variability clearly indicated either a difference in patient selection or technique between sites. The pilot studies also led to the discovery of a problem that had not been foreseen by Emphasys' clinical experts. In

trying to understand why a lobe with complete valve occlusion of all airways sometimes failed to collapse, the Emphasys investigators performed a series of sophisticated tests and determined that the lobes treated with the valves sometimes received sufficient collateral airflow from adjacent lobes to keep that lobe inflated. The team was aware of collateral flow between segments of the lungs (subdivisions within the lobes), but the phenomenon of interlobar airflow had not occurred in sheep, was not anticipated by the pulmonologist advisors, and was not documented in the clinical literature.

In total, investigators treated nearly 100 patients across the pilot sites. In carefully analyzing the resulting data, the statisticians determined that a unilateral procedure worked better than a bilateral one. This finding surprised the group, since a recent national study of LVRS had found that patients did better when the surgery was performed bilaterally. Ultimately, Emphasys determined that a subset of 38 patients who had been treated with unilateral lobe exclusion experienced the greatest volume reduction of the treated lobe. The effect of this could be quantified through two lung function tests, one that measured the amount of air the patient could exhale with force in a single breath in one second (forced air expiratory volume or $FEV_1$) and a measure of exercise tolerance called the six minute walk test (6MWT).

Despite the fact that the company still lacked clearly defined anatomic/disease markers for successful lobe collapse and a standardized selection algorithm, "Our investigators felt we had enough evidence of success and had shown the therapy was safe and well-tolerated by patients," said McCutcheon. "All we wanted was to get into our pivotal and prove this." Gifford added that, "At this point, we really did feel like we had a device that worked and enough predictability about which patients would benefit that we could design the pivotal trial." Most importantly, as Plain pointed out, "Until you do the randomized trial you don't get definitive data." Finally, external pressures came into play for the young start-up. With a burn rate of close to $1 million per month and a number of prospective competitors exploring the space, Emphasys felt compelled to move forward.

The first step in initiating a pivotal study was for Emphasys to apply for an IDE with the FDA. According to McCutcheon, "We were the first company to submit an IDE application in this particular space and the Plastics and Reconstructive Surgery branch didn't have any expertise to evaluate our proposed protocol. Consequently, they brought in two medical reviewers from outside their branch. One was a pulmonologist from the drug division and the other was a thoracic surgeon who consulted for the FDA as a clinical reviewer." From the company's perspective, this created some difficulties. The consultant thought Emphasys should randomize its non-invasive treatment versus LVRS. However, recently published clinical data showed that LVRS had an unacceptably high death rate in high-risk patients. As a result of the article, which appeared in the *New England Journal of Medicine*,[39] LVRS fell out of favor "virtually overnight." "So this was a non-starter for us since it would be impossible to enroll anyone in our trial with LVRS as the control," remembered McCutcheon.

While these discussions were taking place, the FDA convened a panel to help establish the appropriate trial design parameters and clinical endpoints for medical device treatments of emphysema. McCutcheon reiterated, "They'd never seen a device like ours before. Plus, they knew that Spiration, Pulmonx, and Broncus would be coming right behind us [with competitive devices]. So they decided to convene the panel of experts to specify how to design trials for devices like ours: the target patient population, endpoints, control group, and length of follow-up."

In the end, the FDA panel made a series of recommendations regarding the trial design for devices intended to treat emphysema (see Figure 5.3.8). "We were thrilled that the panel advocated the use of medical management rather than LVRS as the control group," McCutcheon commented. Emphasys made minor modifications to its trial design to comply with the other

| # | Recommendations |
|---|---|
| 1 | The trials should include only patients who are candidates for no other procedures or those who have refused other treatments. All patients should have received optimized medical treatment for 3 to 6 months before enrollment. Lung volume reduction surgical patients are not the appropriate control group, and comparisons should be made to patients receiving optimized medical treatment in multi-centered studies. |
| 2 | Safety analyses should include an assessment of deaths, bleeding, mechanical ventilation, pneumonia, air leaks hospital days, re-operations, respiratory failure, decreases in $FEV_1$, 3, 6, 9, and 12 month assessments of device positioning, ease of device removal, COPD exacerbations, intubations, bleeding, and a tabulation of patients who were discontinued due to a lack of benefit. |
| 3 | Effectiveness determinations should include exercise capacity, 6 minute walk test, St. George's Quality of Life Assessment, spirometry ($FEV_1$ increase), decrease in oxygen consumption, and increase in length of life. |
| 4 | The duration of follow-up should continue for at least 6 months for effectiveness and at least 1 year for safety. |

FIGURE 5.3.8
FDA panel recommendations regarding clinical trial design for devices intended to treat emphysema (US Food and Drug Administration).

panel recommendations, and it received IDE approval to proceed with its pivotal study. "However, the surgeon consultant who had advocated using LVRS as the control group never agreed with the panel's decision. This created problems for us later in the review process," McCutcheon said.

Following the FDA guidelines, there would be two primary efficacy endpoints of the Emphasys study: (1) improvement in lung function measured by $FEV_1$ (forced expiratory volume: the amount of air that can be exhaled in one second), and (2) exercise tolerance measured by 6MWT (6 minute walk test: how far a patient can walk on flat surface in six minutes). There was also a primary safety endpoint, which consisted of a major complications composite – that is, a combination of unintended consequences, including respiratory failure, pneumonia or severe bleeding associated with the valves. Patients in the treatment group would receive valve treatment of one targeted lobe to achieve complete lobar exclusion followed by optimal medical management. "Importantly, in retrospect, when the right upper lobe was the target for treatment, the right middle lobe was not treated along with it. Conversely, when the left upper lobe was treated, the treatment included the lingula," noted McCutcheon. Patients in the control **arm** would receive optimal medical management. The individuals in both groups would be given six weeks of pulmonary rehabilitation prior to enrollment to ensure that any post-treatment improvement was not due to the post-procedure rehabilitation regimen. According to the study protocol, the trial was powered to detect a 15 percent improvement in the treatment arm in $FEV_1$ and a 17 percent improvement in the 6MWT, plus or minus a 33.7 and 41.5 percent standard deviation respectively, based on the pilot results. The Emphasys team recruited centers to participate in both the US and Europe.

Because of site-to-site variability observed in the pilot studies, Emphasys went beyond what was required by the FDA to ensure uniform patient selection and targeting, employing a core imaging lab at UCLA to detect and measure important information such as the completeness of the fissures that divide the lungs into lobes. By analyzing this information, the core lab would look for patterns that would help the team more accurately identify which patients to target. While the use of core labs was established and highly regarded in interventional cardiology studies, Emphasys was the first company to use one for a pulmonary study.

Meanwhile, Emphasys continued to work on product development. The original over-the-wire approach to

implanting the valves had been difficult for pulmonologists, who were more accustomed to using a bronchoscope to steer catheters through the lungs. For this reason, the company developed a new variation of its device that could be delivered via the working channel of the bronchoscope. Partway into the pivotal trial, the new system was ready for use. The FDA agreed to the change in the trial protocol but required that Emphasys restart the trial and exclude the 62 patients who had already been treated.

At the end of the pivotal study, 31 trial sites had treated 321 patients with the Emphasys device. However, when the company received the data, some work was required to fully understand the results. "We met the endpoints, but the data were noisy," recalled Greg Bakan, who joined the company as vice president of sales and marketing. While some degree of "noise" was common in all trials, especially one as complex as this, the challenge was in determining its effect on the fundamental outcomes. One of the reasons for this was that emphysema as a disease waxes and wanes, with patients feeling better or worse day-to-day, which could skew their performance on measures such as $FEV_1$ and 6MWT. As with most studies of this magnitude, there was also missing follow-up information for some patients. The follow-up protocol required the collection of literally thousands of data points for each patient, along with extensive lab work, lung function testing, and X-rays. This proved to be a huge burden for many of the chronically ill patients in the study, as even the lung function test maneuvers could provoke an exacerbation of COPD symptoms. "Ultimately, however, our statisticians determined that we had successfully met all of our primary endpoints, both safety and efficacy," said McCutcheon. "Based on that finding, we filed our PMA and were scheduled for panel review in June of 2010." However, in May of 2010, a reviewer contacted the company to notify it that the surgeon consultant on the panel did not believe that Emphasys had met its endpoints. "The message was that we could go ahead to the panel meeting, but that the FDA would tell the panel that we had not met our endpoints, and that we would not be allowed to state that we had," said McCutcheon. "We were told that if we voluntarily withdrew from the panel, the FDA would work with us to resolve these issues."

To better understand the data, and these issues, Emphasys subjected the trial results to a rigorous analysis. According to Gifford, "In those patients for whom we didn't have follow-up data, we needed to impute the results. We had all kinds of sophisticated statisticians look at the data and tell us exactly how we should do the imputations and so on. We spent several months doing that, and no matter how we did it, it came out that our data was statistically significant, showing roughly a 6 percent difference between treated and control patients." Finally, the lead FDA statistician agreed that Emphasys had met its endpoints. "We could now resubmit the PMA in time to make the panel meeting in December of 2010. However, the FDA statistician warned us that the surgical consultant on our panel did not believe that the treatment was clinically significant," said McCutcheon. More than four years (and approximately $75 million) after initiating the pivotal trial, the Emphasys team prepared a clinical report and made its PMA submission to the FDA. "We knew the data was not without its flaws, but we firmly believed it was good enough to get approval," said Mike Carusi, an investor with Advanced Technology Ventures (ATV) and a member of the Emphasys board of directors.

In reflecting on the numerous challenges the team faced in its clinical trials, Plain pointed out that many of these issues are common when a company is pioneering a treatment in a relatively untapped disease area. "It's not like working in interventional cardiology where there's the history of angioplasty that informed stenting and then the history of bare metal stents that informed drug-eluting stents. This was new ground, and frankly, we had to overcome a lot of unknowns," he said. Added McCutcheon, "There were so many hidden variables that not even the experts knew what to expect. So we had to

constantly challenge ourselves and what we thought we knew. But our team was proud to have developed a technology that provided a clinical benefit to a very desperate patient group. Despite all of the ups and downs and struggles with the FDA, we could see the light at the end of the tunnel with the pending panel meeting." Read more about Emphasys Medical's regulatory experience in 5.4 Regulatory Strategy.

## Online Resources

Visit www.ebiodesign.org/5.3 for more content, including:

Activities and links for "Getting Started"

- Determine the purpose of the clinical strategy
- Determine the overall study strategy
- Identify clinical research specialist(s) to work/consult with the internal team
- Choose a trial design/model
- Determine trial endpoints
- Write research protocol
- Decide where to conduct the trail(s)
- Determine resources required to implement protocol
- Understand and implement GCP

Videos on clinical strategy

Appendices that provide:

- A comparison of medtech pilot, pivotal, and post-marketing studies to trials in the pharmaceutical industry
- Further reading on the null hypothesis, type I/type II error, P-values, and sample sizes
- Information about when investigational devices can be used outside an IDE-approved clinical trial

## CREDITS

The editors would like to acknowledge Eric Green, John McCutcheon, Santiago Ocojo, and Allan Will for sharing the case examples. Many thanks also go to Trena Depel and Stacey McCutcheon for their assistance with the chapter.

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