CLINICAL EVALUATION OF MEDICAL DEVICES
Preface

The original edition of this text, *Clinical Evaluation of Medical Devices: Principles and Case Studies*, provided the first overview of key principles and approaches to medical device clinical trials, illustrated with a series of detailed, real-world case studies. The book is designed as a resource for clinical professionals and regulatory specialists working in the field of new medical device development and marketing. Since the first edition of this text was published in 1997, the rapid pace of innovation in health care technologies continues to yield exciting and important new products. The regulatory landscape has also evolved, reflecting some of the changes and needs within the medical device industry.

The purpose of *Clinical Evaluation of Medical Devices: Principles and Case Studies, Second Edition* is to provide an updated and expanded presentation of the scientific methods and regulatory requirements applied to the study of new significant risk medical devices. The text now includes (1) new information on the requirements and process for gaining reimbursement of new products from Medicare and private insurers, with case studies of research specifically designed for this purpose as well as health care technology assessment methods; (2) information on new statistical methodologies applied to medical device trials; and (3) all new case studies, including examples of combination products, three-phase development models (i.e., feasibility, FDA approval, Medicare reimbursement), and novel study designs. This second edition builds on the strength and foundation of the first, and would not have been possible without those colleagues who graciously contributed their expertise in the form of chapters and ideas to the final product.

Karen M. Becker, PhD
John J. Whyte, MD, MPH
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I

FUNDAMENTALS OF CLINICAL STUDY DESIGN AND EVALUATION
Clinical Trials in Development and Marketing of Medical Devices

Karen M. Becker

1. Introduction

Medical devices are health care products distinguished from drugs for regulatory purposes in most countries based on mechanism of action. Unlike drugs, medical devices operate via physical or mechanical means and are not dependent on metabolism to accomplish their primary intended effect. As defined in the federal Food, Drug, and Cosmetic (FD&C) Act, the term *medical device*:

...means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article...intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease...or intended to affect the structure or any function of the body...and which does not achieve its primary intended purposes through chemical action within or on the body."

This broad definition of medical devices encompasses literally tens of thousands of different types of health care products, including in vitro diagnostics. Developing new medical devices and extending the scope of what is known about the performance of already marketed products often requires clinical investigations. Designing well-controlled prospective clinical trials of medical devices presents unique challenges that differ from those faced in studies of pharmaceuticals. For example, clinical outcomes observed in medical device studies are influenced not only by the product under evaluation and the patient, but also by the skill and discretion of the user, who is typically a health care professional but may be the patient. The impact of this third parameter—the medical device user—is a variable unique to medical device studies and can be responsible for the greatest degree of variability in the clinical outcomes. Being aware of and controlling for the user’s influence on device performance is a critical variable that requires attention in designing a clinical study. Other
critical features typically considered in the design of well-controlled studies, such as the choice of a control group, the need to reduce bias, and the need to control for confounders, are common to both drug and device trials; however, the nature of the difficulties presented and the approaches used to successfully address these challenges often differ.

When designing a clinical trial for a medical device, it is useful to consider both regulatory requirements and the manufacturer’s established business goals. The Food and Drug Administration (FDA) is concerned with the safety and efficacy of a product, whereas health care providers and payors are interested in comparative performance, superiority or product differentiation claims, and/or economic data. Therefore, an optimal clinical research program provides not only the data needed for marketing authorization in the United States or abroad but also information to obtain coverage and reimbursement in the targeted markets and support competitive claims.

This chapter provides a detailed discussion of the features of medical devices that can pose challenges in the design of well-controlled clinical studies as well as methods for addressing these design challenges. It also presents an overview of the role of clinical research in the lifecycle of medical device product development and marketing along with the essential elements of a clinical investigational plan for a prospective medical device clinical trial.

2. Drugs vs Devices: Is There a Difference?

The Medical Devices Amendments to the FD&C signed into law in 1976 provided the FDA with broad jurisdiction and authority over the commercialization of medical devices. Before the law’s development, the Secretary of Health and Human Services assembled a task force to consider the nature of the medical device industry in the United States, the extent to which the products of this industry should be subject to regulation, and the best mechanisms for protecting the public health without applying an undue burden to industry or preventing innovation. The task force, known as the Cooper Committee, (after Dr. Theodore Cooper, who had been the director of the National Heart, Lung, and Blood Institute at the time), submitted a report in 1970, the conclusions of which formed the framework of the 1976 legislation.²

The Cooper Committee concluded that medical devices differ significantly from pharmaceuticals, and as such, direct application of the “drug model” of regulation to these products was neither desirable nor feasible. Instead, the committee recommended a novel regulatory approach that was based on the extent of risk posed to the patient from the use of the device. Among the “inherent differences between drugs and devices” ² noted by the Cooper Committee were that medical devices are an extremely diverse group of products varying widely in their intended uses and principles of operation, they are often designed by physicians and subject to frequent innovation in both design and
use, they are used primarily by health care professionals rather than patients, they are most often developed by small companies, and their annual sales are only a fraction of that for a typical pharmaceutical product on a per product basis.

Relying on the Cooper Committee’s recommendations and subsequent testimony, Congress developed legislation incorporating a regulatory pathway for medical devices based on the consideration of the relative risk posed by each product and an apparent acceptance of the principle that the user’s skill and clinical judgment ultimately has a major role in the performance of any particular medical device, regardless of federal regulatory requirements. According to the premarket approval regulations for medical devices, sponsors must provide valid scientific evidence of safety and efficacy. Unlike requirements for drug approvals, this evidence can come from sources other than well-controlled clinical investigations, such as “partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device.” However, the regulation specifically precludes reports of clinical experience that are not adequately supported by data such as anecdotal reports or opinion.

The standard for approval of medical devices is also more flexible than for drugs in that the regulations require “reasonable assurance” of safety and effectiveness, rather than the more onerous burden of “substantial evidence” specified for drugs. Although the FDA’s Center for Devices and Radiological Health has taken responsible and aggressive steps to ensure the rigor of clinical research required to support registration of new medical devices, it has recently reaffirmed the differential standard of evidence for approval of devices vs drugs. As noted by the FDA, the primary practical consequence of the regulations is that the approval requirements for drugs require replication of clinical findings (i.e., more than one clinical trial), but for devices a single pivotal clinical trial is sufficient for approval because, “for medical devices, where the mechanism of action is a result of product design and substantially verified by in vitro performance testing, the agency has routinely relied on single studies evaluated for internal and across-center consistency.”

The differences between drugs and medical devices identified by the Cooper Committee 35 years ago remain valid today, and some are key to understanding features of medical devices that influence product development plans and clinical study design (see Table 1).

2.1. Devices Are Primarily Used by Health Care Professionals

In studies of pharmaceuticals, the two principal interacting variables are the drug and the patient. Given that investigators can control for other variables, such as concomitant exposures, pre-existing conditions, and progression of dis-
ease, the outcomes measured are ultimately a function of the interaction of the drug and the patient. In contrast, the interaction of a medical device and the patient is usually mediated by a third party, the product’s user, who is typically a health care professional. Thus, the clinical outcomes measured in the study of a medical device’s safety and effectiveness are a function of the user’s skill as well as the interaction between the device and the patient. The user, as an intermediary, poses two major difficulties in the design of a clinical trial for devices that are not commonly encountered in studies of pharmaceuticals: Users can rarely be blinded to the treatment intervention and can impact on the product’s performance. Indeed, the user is an integral variable in the performance of the product. A device performs better in the hands of an experienced

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clinical study design issue</th>
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<tbody>
<tr>
<td>Devices are primarily used by health care professionals.</td>
<td>Product performance is influenced by user.</td>
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<td>Devices are subject to frequent incremental innovation.</td>
<td>The user often cannot be blinded to the study intervention.</td>
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<td></td>
<td>Bench testing and animal models alone may validate new designs.</td>
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<td>Some devices are implanted.</td>
<td>Ethical considerations may preclude comparative trials.</td>
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<td></td>
<td>Results from long-term clinical studies may no longer be relevant to current products and medical procedures.</td>
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<tr>
<td></td>
<td>Exposure to the product is not readily terminated or without irreversible consequences to patient.</td>
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<td></td>
<td>Placebo control groups (sham-surgery) are not possible.</td>
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<td></td>
<td>Medically appropriate alternative treatment regimens may not be available to provide randomized, concurrent controls.</td>
</tr>
<tr>
<td></td>
<td>Long-term performance evaluations primarily rely on design controls and failure analysis.</td>
</tr>
<tr>
<td>Devices are often developed by small companies; sales on a per-product basis are less than that for average pharmaceuticals.</td>
<td>Practical considerations (regulations, financial constraints) limit new product development and testing.</td>
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user than in the hands of a naïve user, a phenomenon typically called the *learning curve*. Training in the use of a device is a key part of the investigation of its clinical performance and eventual marketing. If the variability in the user’s proficiency is not accurately assessed or minimized in importance, the device’s performance may be inaccurately estimated.

The inability to blind the user, and often the patient, to the intervention under study can introduce bias into the assessment of clinical performance if the clinical investigator is jointly responsible for treatment and assessment of performance. Thus, whenever possible, blinded evaluators are preferred to clinical investigators in assessing efficacy.

2.2. Devices Are Subject to Frequent, Incremental Innovations

Frequent innovations in the design and use of medical devices are standard practice in the industry. These are often minor modifications that enhance safety, reliability, patient comfort, or ease of use and do not require regulatory approval or premarket notification in most cases. Bench testing and/or evaluations in animal models are often sufficient to validate the suitability of a design change without the need for controlled clinical trials. It is not uncommon for clinicians and Institutional Review Boards (IRBs) to find the results of an in vitro performance evaluation of a new design sufficiently compelling that they are reluctant to proceed with a comparative clinical trial, because continued use of the older design may be deemed unethical. However, clinical studies are usually necessary for design innovations intended to significantly improve performance parameters (efficacy) or to expand indications for use.

2.3. Some Devices Are Implanted

It is estimated that 20 to 25 million people in the United States alone have some type of implanted medical device, such as pacemakers, intraocular lenses, and artificial joints. Some consequences of implanting a medical device are irreversible for the patient, regardless of how long the device is used. Unlike a clinical drug experiment, an implanted medical device trial is not readily terminated. Given that clinical studies of implanted devices are surgical trials, the use of placebo- or sham-operated control groups is usually precluded. Because an ethically appropriate alternative treatment group may be difficult to identify, the use of historical controls in the trial or patients as their own controls (pre- and postsurgery) may be required to evaluate outcomes. Controlled, prospective, long-term performance evaluations of implanted devices (>2 year) are uncommon because they pose logistical constraints (e.g., large sample sizes are required to mitigate against loss to follow-up, inability to identify a sufficient number of suitable patients, expense of a large trial in relation to market size). Instead, information to track rare complications, identify failure modes,
and contribute to enhanced designs is most often collected from the analysis of case series, registries, failure analysis of retrieved devices, bench testing, and formal design reviews.

2.4. Device Manufacturers May Be Small Companies

Medical devices are often products developed by small companies that generate annual sales revenue that is only a fraction of that generated by the average pharmaceutical. A responsible manufacturer conducts whatever testing is required to develop a safe and reliable product, but practical constraints experienced by this particular segment of the health care industry are particularly influential in driving product development and testing decisions.

3. The Role of Clinical Studies in Product Development

Most commonly, the impetus for conducting a clinical study is to demonstrate the safety and effectiveness of an investigational device before marketing, a requirement for registration of implants and other significant risk (SR) devices in the United States and most international markets. An SR device is a product that presents a potential for serious risk to the health, safety, or welfare of a subject and is most commonly an implant or life-sustaining product. The goal of the clinical study is to confirm, validate, or supplement data from bench and/or animal testing. Clinical studies are commonly performed to support a novel design, new technology, and/or new indications for use. However, carefully conceived clinical research also has a role in enhancing product development and marketing for nonsignificant risk products, despite most devices and diagnostics reaching the market after only safety and performance testing in animal models and in vitro. Postmarketing studies can yield information on safety (e.g., long-term safety and performance, uncommon complications), enhance product design, extend labeling claims, and provide data on comparative effectiveness and support for cost–benefit claims. Table 2 summarizes a typical classification scheme for clinical investigations of medical devices.

3.1. Pilot Studies

Pilot studies, or feasibility studies, are usually single-center studies of a limited number of patients designed to accomplish any number of objectives within a clinical-testing program. Pilot studies are not usually designed as hypothesis-testing studies; rather they are intended to generate data in support of the design of rigorous analytical (i.e., hypothesis-testing) trials. The first study of a novel investigational device in humans is usually a small pilot study undertaken to evaluate safety under carefully controlled conditions and to provide data supporting broader performance testing in a larger population. Pilot studies are the
first opportunity to evaluate the role of the user in device performance under actual clinical conditions and gather information on design features that may be modified to optimize proper use of the device. Before designing a pivotal clinical trial to evaluate device safety and effectiveness, pilot studies allow the sponsor to collect data on a series of patient outcomes that may be related to device performance, thereby contributing to the identification and selection of clinically significant measures for use as effectiveness endpoints in a subsequent pivotal trial. Frequently, the selection of measures of safety and effectiveness requires the development of validated assessment methods. More extensive pilot studies can incorporate validation of assessment tools and be used to generate enough data on the interpatient variability of endpoints to support sample-size calculations for use in a hypothesis-testing study.

### 3.2. Pivotal Trials of Safety and Effectiveness

A single, well-controlled clinical trial of device performance remains sufficient for FDA approval of a SR device. These prospective, analytical studies provide objective evidence of effectiveness based on single or multiple clinical outcomes of significance. In combination with data from bench testing and animal studies, results from a single trial are adequate to establish “reasonable evidence” of safety and effectiveness. When direct comparisons are made to alternative treatment options, effectiveness of the new device is expected to be not worse than that of other available devices or treatment. With rare exceptions, pivotal trials in support of successful FDA premarket approval applications (PMAs) are multicentered.

Clinical research conducted on an investigational device before marketing creates the foundation for claims that will appear on its label once marketing authorization is accomplished. This point is especially critical in the United States, where the expectations for reliable data in support of all aspects of the label are the most rigorous. For this reason, the clinical portion of the product

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**Table 2**

**Typical Classification of Medical Device Clinical Studies**

<table>
<thead>
<tr>
<th>Classification</th>
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<tbody>
<tr>
<td>Pilot studies of safety, performance, and/or design before marketing</td>
</tr>
<tr>
<td>Pivotal trials of safety and effectiveness before marketing</td>
</tr>
<tr>
<td>Postmarketing studies</td>
</tr>
<tr>
<td>In support of expanded labeling claims</td>
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<tr>
<td>In support of comparative performance claims</td>
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<tr>
<td>Pharmacoeconomic studies</td>
</tr>
<tr>
<td>Observational or analytical studies of specific safety or performance issues</td>
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<tr>
<td>Explant retrieval and failure analysis investigations</td>
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</tbody>
</table>

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development plan should never be considered in isolation from the ultimate marketing goal. In some cases, bench testing and animal studies can provide additional performance data to augment the clinical research and support expanded label claims.

3.3. Postmarketing Studies

Two categories of postmarketing studies can be distinguished: mandated postapproval studies and postmarket surveillance studies. It has become increasingly common for the FDA to require sponsors of Class III devices to conduct a postapproval clinical study as a mandatory condition of PMA approval. These studies are usually narrow in scope and focus on generating additional data to expand on results of the pivotal trial(s) in support of product approval. The objectives of postapproval studies, whether mandated by a regulatory agency or the state of the science, typically include longer-term follow-up, additional data on the incidence and time-course to appearance of adverse events, and additional data in support of broader label claims (e.g., indications for use, duration of effectiveness, product benefits). Postapproval studies may be undertaken as an extension of a pivotal trial via protocol amendments to extend follow-up or they may be conceived as an entirely separate study. The trend toward mandatory postapproval studies reflects the FDA’s commitment to work with sponsors whose investigational plans were finalized before 1993, when the agency shifted to a more rigorous standard of clinical trial requirements.6,10,11 Careful consideration of pivotal trial design and good communication with the FDA in the design of investigational plans before initiation of pivotal clinical trials will likely minimize the need for mandatory postapproval studies.

Distinct from postapproval studies are the various types of postmarketing studies undertaken by a manufacturer to accomplish a variety of goals. These studies may be sponsor-initiated or required by a regulatory agency in response to a perceived safety concern. The federal Safe Medical Devices Act of 1990 and the FDA Modernization Act of 1997 (FDAMA) empowered the FDA to require mandatory postmarket surveillance trials for certain types of devices as well as discretionary postmarket surveillance trials. Under FDAMA, the FDA can require companies to conduct postmarket surveillance studies for Class II or Class III devices under the following conditions:

1. The failure of the device would be reasonably likely to result in serious health concerns.
2. The device is intended for implantation in the human body for a period greater than 1 year.
3. The device is a life-sustaining or life-supporting product that is used outside a device user facility.
Mandatory postmarket surveillance trials to date have been directed at developing systematic data on either long-term failure modes and/or the potential for serious adverse events occurring in a small number of patients receiving devices (e.g., heart valves, injectable collagen, polyurethane breast implants, pacemaker leads). Compliance with Quality System Regulations for medical devices requires manufacturers to engage in postmarket surveillance monitoring of marketed products. This includes requirements to evaluate and act on complaints, product failures, and adverse events associated with product use. This is not a passive process; the responsible manufacturer maintains routine procedures for systematic evaluation of postmarket experience directed toward investigating product failures and successes and may include research (bench testing or clinical) to improve product performance and safety.

In addition to meeting regulatory requirements, other goals of postmarket research, including comparative studies with alternative or competitive treatments and/or devices, may be to provide support for pharmacoeconomic claims, comparative effectiveness claims, or expanded label claims. As previously noted, implanted device studies in which patients are followed prospectively for more than 2 years are not generally practical because of the loss of follow-up, enormous expense, and rapidly progressing changes in medical practice. Carefully considered programs to exploit explant analysis and failure investigations, coupled with design controls before marketing, are the most common, effective, and efficient means of gathering data on long-term performance. Sponsors are also beginning to use observational studies effectively for retrospective studies of clinical experience, especially when the goal is to gather data on patient- or device-specific factors that may contribute to long-term performance failures. As with pharmaceuticals, vigilance in the evaluation of adverse events reports, returned goods, and complaints are important sources of information on clinical experience. Although anecdotal, these data are the foundation for research into design deficiencies and strengths and may lead to products that perform better.

4. Elements of a Clinical Investigational Plan

Clinical research studies can be categorized as either observational or analytical. An observational study is designed to collect and analyze data on subject exposure or treatment interventions and does not include a control group. The investigators collect, record, and analyze data to generate or test a hypothesis. Examples of observational studies that are designed to collect data include daily recording of rainfall and temperature, surveys of dietary intake, and data on national cancer incidence. Observational studies are valuable when an experimental approach is not practical or is otherwise unfeasible.
Analytical studies are hypothesis-testing trials comprised of a cohort exposed to a specific intervention, the impact of which is subsequently assessed. The “gold standard” of analytical clinical trial design is the prospective, randomized study with concurrent control group(s). The reader is referred to several excellent sources for detailed discussions of the principles of good clinical study design, conduct, and analysis. Although generally written from the point of view of pharmaceuticals, the principles of good clinical study design apply equally to both drugs and devices.\textsuperscript{12–16}

Clinical protocols for medical device trials typically incorporate a device description and a patient-risk analysis along with information describing the design, conduct, and analysis of the planned trial. The essential elements of a clinical investigational plan are listed in Table 3. Each of these is considered in the following discussion, with particular emphasis on features that may be problematic for medical devices.

### Table 3

**Elements of the Investigational Plan**

<table>
<thead>
<tr>
<th>Device description</th>
<th>Study objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Study population</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td>Control group</td>
</tr>
<tr>
<td>Endpoints evaluated</td>
<td></td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Safety</td>
</tr>
<tr>
<td>Definition of trial success (if hypothesis-testing study)</td>
<td>Study procedures and duration</td>
</tr>
<tr>
<td>Screening and assignment to treatment</td>
<td>Assessments and follow-up</td>
</tr>
<tr>
<td>Training procedures (if appropriate)</td>
<td>Sample-size calculations</td>
</tr>
<tr>
<td>Data analysis plan</td>
<td>Risk analysis</td>
</tr>
<tr>
<td>Case report forms</td>
<td>Informed consent forms</td>
</tr>
<tr>
<td>Investigational site(s) and IRB information</td>
<td>Data safety monitoring board (optional)</td>
</tr>
<tr>
<td>Monitoring plan</td>
<td>IRB, Institutional Review Board.</td>
</tr>
</tbody>
</table>

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4.1. Device Description

A description of the product under investigation is provided with sufficient information for the clinical investigators to understand the design of the device, the rationale in support of the product design (which may include references to preclinical testing), device performance specifications, a statement of intended use, and the instructions for use.

4.2. Study Objective

Before designing a clinical study, it is necessary to clearly formulate the question(s) to be answered by the research effort. It should be possible to prepare a summary statement of the objective for any protocol by noting four features for the study:

1. The product tested.
2. The indication for use (treatment or condition to be affected).
3. The primary outcome measure.
4. The subject characteristics (e.g., disease stage).

4.3. Study Design

The clinical study design specifies whether the study is prospective or retrospective, open-label (nonblinded) or controlled, and single-center or multicenter. Although the simplest controlled design includes two groups of subjects, controlled trials may have many variations (e.g., crossover studies, sequential studies). More than two groups of subjects result in a multiple-arm trial, a design that may be selected to incorporate a sham- as well as an active-control group. It is generally best to choose the least complicated design required to successfully address the trial objective. For more information on clinical trial design, refer to the Spilker textbook.

4.4. Study Population

In addition to articulating the clinical condition of the subjects, investigators often include demographic criteria specifying patient age, sex, and race. Economic status or educational level may be relevant; for instance, this data may useful in trials evaluating the labeling and instructions for use of over-the-counter in vitro diagnostics. Defining specific subject inclusion and exclusion criteria is an important means of narrowing the range of subjects studied, thereby minimizing the impact of uncontrolled variables and variability in the effectiveness and safety endpoints observed. For a pivotal clinical trial intended to support FDA approval, the definition of the patient population is significant because the approved PMA will generally have a label, which only supports use in the study population evaluated.
4.5. Treatment Regimen

The nature of the intervention under study encompasses a description of the device, instructions for use, and any other ancillary or related procedure or treatments. For surgical trials, it is especially critical to work with clinical investigators at all sites to develop a consensus to the greatest extent possible on surgical procedures to be used. Uniformity of procedures across sites, coupled with training of clinical investigators and their staff, are the two most critical techniques used to reduce variability and site-specific bias. For devices that represent a truly novel innovation and for which investigators are not expected to have significant first-hand experience, trials can include a prespecified run-in period to stratify sequential procedures as a function of investigator experience and thereby evaluate the impact of the learning curve on device performance.

4.6. Control Group

The control group serves as a benchmark for gaging safety and effectiveness of the device and allows investigators to estimate the clinical significance of device’s effect in a defined patient population. By definition, the control group comprises a set of patients or subjects who are not exposed to the intervention or device.

There are two broad categories of control groups: concurrent controls and nonconcurrent controls. Concurrent controls are subjects assigned to a control exposure and observed contemporaneously with the experimental group. The control exposure may be no treatment at all, treatment with a placebo, or treatment with an alternative therapy or device. Concurrent controls are always the preferred choice. Using a concurrent control group allows trial subjects to be randomized between control and treatment groups, thereby eliminating selection bias and controlling for confounding variables.

Nonconcurrent controls are subjects who are not observed contemporaneously with the experimental group. The most common nonconcurrent control is the historical control group, comprising a cohort previously observed, treated, studied, or reported on. Historical control groups must be used with caution, because the quality of the historical data set is often variable and may be unreliable. The subjects in the historical cohort may not be comparable to those in the treatment group in terms of demographics or disease status, and confounding variables cannot be controlled through randomization. Furthermore, because the nature and success of medical treatments tend to improve over time, historical cohorts are more likely to bias the results of a trial toward a positive outcome.
Although the choice of the proper control group is driven by the objectives of the trial and should be supported by a sound rationale, ethical and practical constraints impact the decision. It is not uncommon to discover that the ideal control group from a scientific point of view is not always feasible for logistical or ethical reasons (e.g., a sham-operated control in a surgical trial). Well-controlled studies of some implants can be conducted with the patients as their own controls if an alternative device or procedure is not available. Historical controls should be used only if the quality of the data set is deemed to be reliable and valid, and if the pathogenesis of the disease under study is well understood. They may also be used when the objectives of the trial are limited (e.g., feasibility study).

4.7. Effectiveness and Safety Endpoints

The protocol should specify the clinical endpoint to be assessed in the evaluation of device effectiveness. The selection of the primary effectiveness endpoint is critical to the success of the trial. An appropriate endpoint is a clinically significant outcome that can be measured using a validated method. For a hypothesis-testing study, the extent of change compared to control should be projected to be large enough to have a clinically significant impact on the patient in terms of quality of life, disease progression, diagnosis, or mitigation. Although it is most common to use a single, primary endpoint, some trials may incorporate multiple primary endpoints, with the goal being to demonstrate a clinically significant response through several measures. Secondary endpoints can provide additional data to support product claims, confirm effectiveness, and aid in establishing the reimbursement strategy.

Data on safety and adverse events associated with the studied intervention should be collected as broadly as possible. Previous clinical experience with the device and/or data from nonclinical studies highlight specific safety issues that should be considered in a clinical trial; however, these targeted evaluations do not preclude the need to capture all data on observed adverse events, regardless of whether they are deemed to be device-related at the time.

4.8. Definition of Trial Success

If the clinical trial is a hypothesis-testing study, it is powered to detect a clinically meaningful difference in treatment and control. This is usually expressed as the magnitude of some clinical outcome deemed to be sufficient to conclude that the device is effective in comparison to a baseline value and/or the control group response. In the United States, demonstrations of device effectiveness do not require that the new device be superior to existing products; instead, it is acceptable for product performance to be not worse than the standard alternative treatment(s).
4.9. Study Procedures and Duration

This section of the protocol describes the conduct and duration of the study, including screening procedures, scope of the initial patient work-ups, schedules and procedures for follow-up visits, and procedures for discontinuations. The procedures for assigning subjects to the intervention (i.e., randomization scheme) must also be included.

Standardized training procedures for using the device are important features of well-controlled studies of medical devices. Training programs enhance the rigor of a trial by minimizing bias and the impact of confounding variables on device performance that often result from variability in individual user skill and discretion. The extent of training provided to users in a clinical trial varies, and extensive training may appropriately raise questions regarding the extent of training that a manufacturer should provide once marketing commences. In certain trials (e.g., for over-the-counter in vitro diagnostics), it is appropriate not to provide training in the use of the device in order to simulate the actual conditions of use.

4.10. Sample-Size Calculation and Data Analysis Plan

The number of subjects selected for inclusion in a hypothesis-testing study should be justified by sample-size calculations that specify the statistical power of the study. To calculate sample sizes, it is necessary to define the number of subjects specified by the underlying statistical model selected. Usually these parameters include the magnitude of the anticipated outcome resulting from the intervention under study, the variability in the measure of that outcome, the desired power of the study (usually 80%), and the statistical significance (most often 95%). The statistical approach to be used in the analysis of the data collected is articulated in the data-analysis plan. Consultation and collaboration with an expert statistician is necessary to address these aspects of the protocol.

4.11. Risk Analysis

The risk analysis describes the potential risks and benefits to the study subjects in sufficient detail to provide adequate informed consent and support the conclusion that the risks to the patients are not unreasonable. The risk analysis includes a description of alternative procedures available, a consideration of potential failure modes, the steps taken in the design of the device and the trial to minimize risks to the trial subjects, and the rationale for the anticipated benefit to the patient.

4.12. Informed Consent Forms

Informed consent materials given to study subjects should provide complete information on the procedure and its potential risks in a format that is easy to
read and understand. The informed consent form should be explicit regarding the voluntary nature of the subject’s participation, the known and potential risks and benefits of participation, and the subject’s willingness to participate in all required aspects of the study. Regulatory authorities throughout the world require adequate informed consent from clinical trial subjects.\textsuperscript{17–19}

### 4.13. Case Report Forms

Each trial must include case report forms to record the data collected on each subject in accordance with the study protocol. These forms contain information on subject screening, operative information, postoperative and follow-up visit data, adverse event reports, and subject withdrawal forms.

### 4.14. Investigational Site(s) and Institutional Review Board Approvals

The investigational plan specifies the investigational site(s) involved in the study and includes information on the qualifications of the clinical investigators, the IRB procedures, and records of IRB approvals.

### 4.15. Investigator’s Brochure

The goal of the investigator’s brochure is to provide the investigator with a thorough understanding of the risks and adverse reactions associated with the device, as well as a detailed description of the device and how it functions. The topics addressed in the investigator’s brochure include:

1. A summary of the literature.
2. A summary of previous clinical research.
3. A description of the device.
4. Device hazards and risk analysis.
5. Device performance and preclinical testing.
7. Reported adverse events.

### 4.16. Data Safety Monitoring Board

In certain circumstances, a sponsor will elect to establish a Data Safety Monitoring Board comprised of experts who continually evaluate the safety data accrued in a study. This is most common for early clinical experience with an investigational device or studies in which significant morbidity or mortality is expected. In either case, the monitoring of safety data while a study is ongoing is blinded and intended to minimize risks to the patients by providing a system to alert investigators to unexpected adverse outcomes that may require premature termination of a trial. Alternatively, if a treatment is unexpectedly robust in terms of efficacy, a trial may be terminated early on the grounds that continuing the study would be unethical given the benefit provided to the treatment group.
4.17. Monitoring Plan

A clinical trial monitoring plan defines the procedures that the sponsor or his or her representative will undertake to provide quality assurance in the study’s conduct. The monitoring plan ensures that the study is conducted in accordance with the procedures specified in the protocol. The importance of a carefully designed and implemented monitoring plan cannot be overstated. This aspect of study conduct ensures that the data generated from the trial are valid, serves to identify early in the study any significant problems that may arise, and helps ensure that the eventual audit of the clinical study by regulatory authorities is satisfactory.

5. Conclusions

Well-controlled clinical trials of medical devices have become the standard in the industry for the premarket evaluation of new products and systematic evaluations of performance for products already on the market. The basic principles of good clinical study design developed for trials of pharmaceuticals provide the best foundation for the design of trials of medical devices. Although it is common to discover in the design of a prospective, analytical study of a medical device that there are unexpected sources of bias and confounders that require adjustments to the clinical trial strategy, rigorous studies can be developed using innovative or alternative methods. A successful clinical investigation requires careful planning to clearly delineate a testable hypothesis and to select:

1. A study design that can support the required analysis.
2. A suitable control group.
3. Primary outcome measures that are objective, validated, and clinically relevant.

It is important to remember that some questions regarding safety and effectiveness of medical devices are not readily answered in prospective, controlled clinical studies—especially for implanted devices. Most notably, it is necessary to rely on a combination of data from bench testing, animal studies, device-retrieval analysis, and observational research to ascertain with some degree of confidence the anticipated durations of in vivo performance, failure modes, and long-term fate of implanted materials.

References

Regulatory Requirements for Clinical Studies of Medical Devices and Diagnostics

Daniel A. Kracov and Lisa M. Dwyer

1. Introduction

The investigational device exemption (IDE) provides an release for medical devices from various sections of the federal Food, Drug, and Cosmetic (FD&C) Act. Without the exemption, medical devices would have to comply with performance standard, premarket approval, or notification requirements to be lawfully shipped and used for investigational purposes. Furthermore, it would be exceedingly difficult—if not impossible—to conduct clinical trials for devices to support premarket approval applications (PMAs) or 510(k) premarket notifications without violating the act, if the IDE did not exist. Indeed, according to Congress and the Food and Drug Administration (FDA), the twin objectives of the exemption are “to encourage discovery and development of useful devices for human use” and “to protect the public health by requiring safeguards for human subjects of investigations, sound ethical standards, and procedures to assure development of reliable scientific data.”

1.1. Brief History of Clinical Trial Regulation of Devices

The IDE was enacted as part of the Medical Device Amendments of 1976 (“the Amendments”). As the FDA had regulated the investigational use of new drugs and biologics for years, it was widely recognized that the new framework for medical device regulation required a corresponding—if not equivalent—framework for controlling investigational devices. The statutory provision granting the exemption, which can be found in Section 520(g) of the FD&C Act, expressly authorized the Secretary of what was then called the Department of Health, Education and Welfare to regulate the investigational use of medical devices.
Notably, Section 520(g) required the agency to issue regulations within 120 days of the effective date of the 1976 Amendments. These regulations are now found in 21 C.F.R. Part 812. Although the IDE regulations vary from the investigational new drug regulations, they are substantively similar in many respects. One fundamental difference, however, is that Section 520(g) of the act expressly permits FDA to vary the procedures and conditions of the regulation of investigational devices based on the nature of the device, the scope and duration of the trial, the number of human subjects involved, the need for changes to be made in the device during the investigation, and whether the purpose of the data is to obtain approval to commercially distribute the device.

1.2. Investigational Devices Subject to Regulation

Clinical investigations for most new devices or for new uses of devices are subject to the IDE regulations in 21 C.F.R. Part 812. However, FDA exempted clinical investigations for the following types of devices:

1. Pre-1976 Amendment devices that currently are being investigated for the same indications that existed before the 1976 Amendments.
2. Post-1976 Amendment devices that are being investigated for purposes that have been cleared through the 510(k) premarket notification process.
3. Diagnostic devices that meet certain requirements.
4. Devices undergoing consumer preference testing and other similar types of testing if the testing is not used to determine safety and efficacy and does not put subjects at risk.
5. Devices intended solely for veterinary use.
6. Devices being tested solely on or with laboratory animals.
7. Custom devices.

1.3. Structure of FDA Regulation of the Investigational Device Exemption

As mentioned, the IDE regulations permit sponsors to conduct clinical studies on new devices or new device indications to collect the requisite safety and efficacy data to support PMAs and, in some instances, 510(k) premarket notifications. The IDE regulations establish minimum requirements that must be met before an investigational device study begins. For example, the sponsor of any clinical device investigation must obtain approval from an Institutional Review Board (IRB) and informed consent from study subjects before the study begins.

If the investigational device poses a serious risk to the health, safety, or welfare of a subject (i.e., a significant risk [SR] device), the sponsor also must obtain FDA’s approval of the IDE application. The IDE application must contain information concerning the study’s investigational plan, prior investigations, device manufacture, IRB actions, investigator agreements, the subjects’ informed consent forms, device labeling, the cost of the device, and other
matters related to the study. FDA has 30 calendar days from the date it receives the application to approve or disapprove the application.  

2. Regulations Relating to People and Institutions Engaged in Clinical Trials

The FDA has promulgated a number of regulations delineating the responsibilities of the key players involved in clinical trials for devices (i.e., sponsors, investigators, IRBs).

2.1. Sponsors

A sponsor is a person, an institution, or a company that initiates, but does not actually conduct, an investigation. Importantly, a sponsor is distinct from a sponsor-investigator, who both initiates and actually conducts or oversees an investigation. Sponsor-investigators must comply with FDA’s regulations for both sponsors and investigators.

FDA’s regulations provide that sponsors generally are responsible for the following: (1) selecting investigators (i.e., individuals who actually conduct an investigation), (2) providing investigators with necessary information to conduct the investigation, (3) ensuring proper monitoring of the investigation, (4) ensuring that the IRB review and approval are obtained, (5) submitting an IDE application to FDA, and (6) ensuring that any reviewing IRB and FDA are promptly informed of any significant new information about an investigation. Sponsors must also comply with the labeling, reporting, and record-keeping requirements established in 21 C.F.R. Part 812 and refrain from engaging in promotional activities and the other prohibited activities enumerated in 21 C.F.R. §812.7 (e.g., commercializing an investigational device).

FDA regularly issues warning letters to sponsors who fail to comply with these general responsibilities. For example, on October 3, 2003, FDA sent a warning letter to an orthopedic device company that sponsored a device investigation regarding its failure to comply with its responsibilities in Part 812 of the regulations. Among violations mentioned in the warning letter, the company failed to submit an IDE application, failed to ensure that investigators received IRB approval before use of the investigational device, and failed to ensure proper monitoring of the study. As a result, 31 devices (the name of which has been redacted from the warning letter) were implanted in research subjects without FDA and IRB approval. Of those 31 devices, 12 devices were implanted using a procedure or instrument that was not part of the investigational plan, and nine devices were implanted in patients not enrolled in the study. Moreover, the warning letter cited a number of additional deviations from the IDE regulations. This warning letter demonstrates how failure to comply with the IDE regulations can expose patients—even those not enrolled in the study—to uncontrolled situations that may present unnecessary risks.
2.1.1. Transfer of Sponsorship

To transfer sponsorship to another person, a sponsor must submit a minimum amount of information in the form of an IDE supplement to FDA. Once FDA has acknowledged the transfer, the agency must request additional information. To streamline the process, original and new sponsors may want to consider submitting the minimum information required for acknowledgement of the transfer and the information in response to the required follow-up questions in the initial IDE supplement notifying the agency of the transfer. Table 1 summarizes the information required for the transfer of sponsorship in the initial IDE supplement and in response to FDA’s follow-up questions.

### Table 1

**Information Required for Transfer of Sponsorship**

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<thead>
<tr>
<th>Minimum information required for transfer&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td>• Identification of the new sponsor (e.g., name, address, contact person, telephone number)</td>
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<tr>
<td>• Effective date of transfer</td>
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<tr>
<td>• Certification that all relevant records will be transferred to the new sponsor by the effective date of the transfer</td>
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<tr>
<td>• An agreement from the new sponsor, stating that the new sponsor will assume all sponsor responsibilities for the study</td>
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<tr>
<td>• An agreement from the new sponsor, stating that the new sponsor will comply with any terms or outstanding conditions of approval of the investigation</td>
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<tr>
<th>Additional information requested by FDA after transfer&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td>• A statement: that there are no changes in the investigation caused by the transfer or requesting specific approval for changes in the investigation that could affect the scientific soundness of the investigation or the rights, safety, and welfare of the subjects</td>
</tr>
<tr>
<td>• Acknowledgment that all investigators and associated IRBs will be informed of the sponsorship change by the effective date</td>
</tr>
<tr>
<td>• Certification that the new sponsor will not permit investigators to participate in the investigation until they have signed the investigator agreement.</td>
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</table>

<sup>a</sup>See id.

### 2.2. Investigators

An investigator is an individual who actually conducts a clinical investigation (i.e., the person who directly oversees the administration of a device to a