Clinical Trial Requirements for Cardiac Devices

43

Jenna C. Iaizzo

Abstract

Early medical device concepts that show promising safety and/or efficacy results in preclinical trials, bench top testing (including accelerated wear testing), a virtual prototyping environment, and/or computation modeling studies will eventually be implanted in humans. Currently in the United States, the required time to develop a new cardiac device and gain approval for market release is highly dependent on the time it takes to perform proper clinical trials, i.e., to receive the needed clearance or approval from the Federal Drug Administration.

Keywords

Clinical trial • Cardiac devices • Regulatory agency • Food and Drug Administration

Abbreviations

CE	Conformité Européenne or European Conformity
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EOA	Effective orifice area
FDA	Federal Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISO	International Organization for Standardization
OPC	Objective performance criteria
PMA	Premarket approval

J.C. Iaizzo, MBA (✉)
Medtronic, Inc., Minneapolis, MN 55428, USA
e-mail: jiaizzo@gmail.com

43.1 Introduction

Clinical trials play a crucial role in the process of bringing medical devices, specifically cardiac devices, to the market and for providing continued scientific clinical data after commercialization (Fig. 43.1). Prior to executing a clinical trial, researchers, scientists, and engineers cannot predict how the newly developed devices will perform in a human body. Furthermore, most cardiac devices are typically class III life-sustaining devices that are implanted in patients with life-threatening conditions, but there is a broad spectrum of the patients receiving these therapies that will likely have many other clinical complications; in some cases, these complications may adversely affect the potential success of novel technologies. Therefore, carrying out a carefully designed and comprehensive clinical trial provides an significant opportunity to examine the outcomes of the new cardiac device in humans and, in turn, the resultant clinical data gives patients, physicians, and the entire scientific community the information needed to potentially use the new device. Yet today, the primary purpose of a clinical trial is to provide valid scientific data about the safety and/or efficacy of a device, resulting in clinical evidence for future use or retraction of a therapy.

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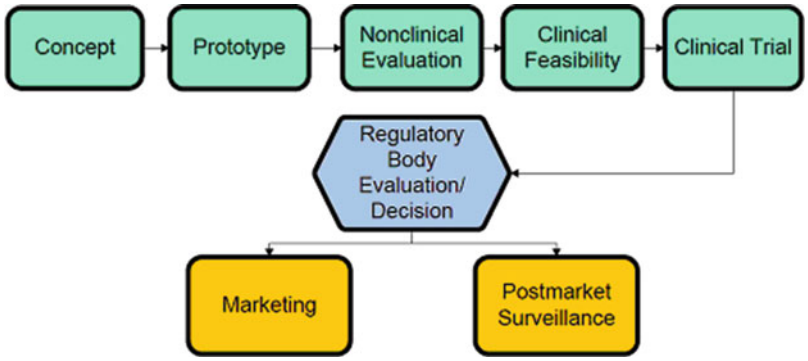

Fig. 43.1 Timeline of medical device development ©2013 Heart Valves: From Design to Clinical Implantation, Clinical trial requirements for cardiac valves, Iaizzo JC, Lovas ATF. With kind permission of Springer Science+Business Media, New York

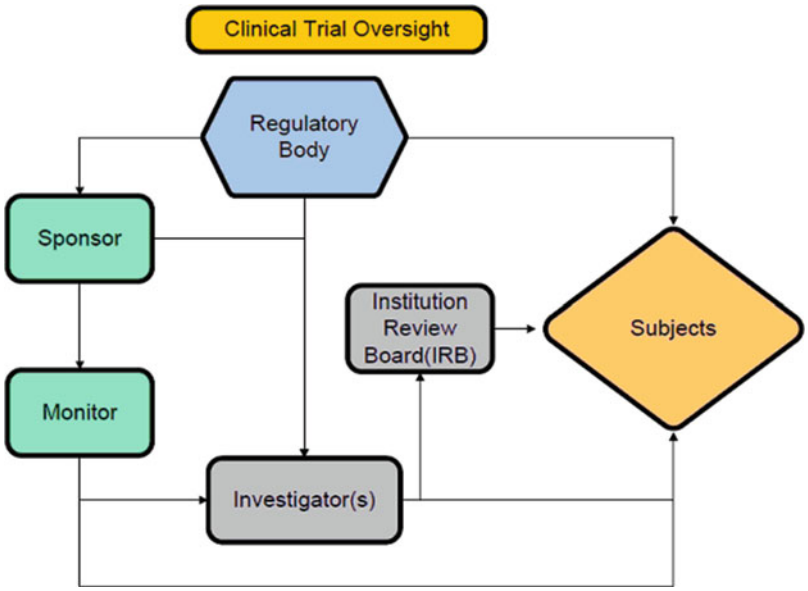

Fig. 43.2 Clinical trial oversight ©2013 Heart Valves: From Design to Clinical Implantation, Clinical trial requirements for cardiac valves, Iaizzo JC, Lovas ATF. With kind permission of Springer Science+Business Media, New York

With the diversity of cardiac devices, there are various types of clinical trials that can be defined, from trials where a novel valve technology is being used for the first time (*first in human* studies) to post-market trials in which a cardiac therapy has obtained regulatory approval but is studied further to examine long-term effects, pursue additional indications, and/or to obtain more specific information about the overall therapy. In other words, clinical evidence is vital not only to demonstrate the safety and efficacy of a device/therapy in humans but also to further examine how well the device works compared to standard of care, other devices, and/or concomitant treatments. In the specific case of a newly developed heart valve, studies will often be designed to compare the new valve against the native valve, other heart valve devices, and/or the current standard of care treatments. Using the example of planning a clinical trial for a new heart valve, this chapter provides a general summary of the present state of clinical trials, including an overview of (1) the current stance of regulatory bodies that oversee trials, (2) specific features of a trial design, and (3) the many considerations involved in the proper implementation of heart valve clinical trials.

Regarding the design of a clinical trial, the following groups/individuals may be identified, each with their specific role(s) (Fig. 43.2):

***Sponsor*(*s*)**: The developer of the technology seeking approval for market release.

***Investigator*(*s*)**: Non-biased individuals that will implant/deploy the novel technology and will also be responsible for individual patient follow-ups. In some cases, investigators can also develop their own field clinical trial(s).

***Monitor*(*s*)**: Individuals responsible to ensure that the trial is performed in an ethical and proper fashion. They usually work for the sponsor and make frequent visits to participating institutions to review data and regulatory documents.

Regulatory bodies also have their own process for auditing sponsors and investigators through their Bioresearch Monitoring group(s).

***Institutional Review Board* (*IRB*)/*Ethics Committee* (*EC*)**: The overseeing body at a given institution that is ultimately responsible for ensuring that the clinical protocol is appropriate and that the institutional investigators perform the study in a proper and ethical manner. These boards may have different names according to the institutional structure.

Subjects: Individual patients who were deemed appropriate to be enrolled (meeting all inclusion criteria and none of the exclusion criteria) into the planned clinical trial and who provided informed consent to participate.

43.2 Regulatory Bodies

Regulations and the regulatory bodies that govern both cardiac devices and clinical trials play important roles in how new technologies reach the market. A solid partnership between a sponsor and a regulatory body, aided by clear communication, can affect whether the technology can reach the market in an expeditious manner. Regulatory bodies are important, as they ensure consistency in clinical trials and that they are run properly in order to provide the supportive scientific evidence required. Specifically, there are numerous regulatory bodies that provide oversight for cardiac device clinical trials throughout the world. A brief overview of the regulatory bodies from three different countries follows, yet our discussion focuses mainly on the Food and Drug Administration (FDA) in the United States.

43.2.1 Food and Drug Administration (United States)

The FDA is responsible for regulating medical devices and therefore oversees the associated clinical trials exclusively within the United States. The FDA's mission statement consists of two primary parts: (1) promoting public health by promptly and efficiently reviewing clinical research and taking appropriate action on marketing of regulated products in a timely manner and (2) protecting public health by ensuring a reasonable assurance of safety and effectiveness of devices intended for human uses [1]. The Center for Devices and Radiological Health (CDRH) is the branch that oversees medical devices. Cardiac devices that incorporate other therapies (i.e., pharmacological agents) will need to confirm if they will work through CDRH and/or the Center for Drug Evaluation and Research (CDER).

In the United States, there are three regulatory classes of devices based on the considered levels of risk involved. All class I–III devices are subject to general controls, meaning the FDA reviews factors such as labeling, registrations, etc. Class I devices have the lowest amount of risk and regulatory controls (devices such as elastic bandages and surgical gloves). Class II devices must meet specific performance standards in addition to all class I requirements (devices such as surgical drapes). Most stringently, class III devices require premarket approval (PMA) to ensure their safety and efficacy. As such, class III devices are considered as the riskiest category of devices and include devices such as implantable pacemakers and heart valves.

It should be noted that the FDA regulations for medical device products are detailed in Title 21 of the Code of Federal Regulations (CFR). The most applicable parts of CFR 21 that apply to cardiac devices and clinical trials include Part 812 (Investigational Device Exemption, or IDE) and Part 814 (PMA). Most new and novel cardiac devices are required to undergo IDE clinical trials before receiving FDA approval. As the regulatory landscape is typically in constant flux, it is crucial to reference and follow current guidance and regulations set forth by the respective governing regulatory body.

In the example of heart valves, there is specific guidance in documents like the FDA's Heart Valves—IDE and PMA Applications Draft Guidance; these documents state that "a replacement heart valve is a device intended to perform the function of any of the heart's natural valves" [2]. A replacement heart valve is defined as a pre-amendment-type device, that is, a device marketed prior to passage of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (the Act).

Furthermore, this FDA draft explains that clinical trials are necessary to evaluate most new replacement heart valve designs, and it also recommends that clinical investigations are executed by following the methods described in ISO 5840:2005 or an equivalent document. Specifically, the document ISO 5840:2005 is a guide for cardiovascular implants and valve prostheses provided by the International Organization for Standardization (ISO) [3]. When developing a clinical database and trial strategy, the appropriate FDA guidance should be referenced.

43.2.2 Other Regulatory Bodies

In Europe there are various *notified bodies* that provide oversight of clinical trials. The most prevalent regulatory oversight applies to the 27 countries in the European Economic Area; these are countries required to obtain a *CE mark* (Conformité Européenne or European Conformity). Importantly, the criteria to receive a CE mark in Europe are notably different than those for securing FDA approval. As mentioned previously, to receive approval for a new technology in the United States, the manufacturer must demonstrate the device to be reasonably safe and effective. To receive approval to release a device to market in the European Union, the manufacturer must demonstrate that the medical

device is safe and that it performs in a manner consistent with the manufacturer's intended use [4]. Interestingly, given these differences in geographic regulatory approval, most manufacturers typically seek approval in Europe or other countries before the United States. Moving into other countries poses different obstacles which may influence the intended quality and importance of every clinical trial completed for the new device.

43.2.3 Good Clinical Practice Oversight

Similar to the importance of following Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) when prototyping cardiac devices, it is important to follow guidelines for how to appropriately conduct clinical studies that could affect the safety and well-being of human participants. Good Clinical Practice (GCP) was developed by a collaborative group of regulatory authorities worldwide, including the European Union, Japan, and the United States by the International Conference on Harmonisation. Effective in 1997, GCP provides international assurance that data and results of clinical investigations are credible and accurate and that the rights, safety, and confidentiality of participants in clinical research studies are respected and protected. More specifically, GCP consists of 13 principles which are detailed in Table 43.1.

Table 43.1 13 Principles of good clinical practice [5]

Ethics
1. Ethical conduct of clinical trials
2. Benefits justify risks
3. Rights, safety, and well-being of subject prevail
Protocol and science
4. Nonclinical and clinical information supports the trial
5. Compliance with a scientifically sound, detailed protocol
Responsibilities
6. Institutional Review Board/Independent Ethics Committee approval prior to initiation
7. Medical care and decisions by qualified physicians
8. Each individual qualified (education, training, experience) to perform his/her tasks
Informed consent
9. Freely given from every subject prior to participation
Data quality and integrity
10. Accurate reporting, interpretation, and verification
11. Protects confidentiality of records
Investigational products
12. Conform to Good Manufacturing Practice and used per protocol
Quality control/quality assurance
13. Systems with procedures to ensure quality of every aspect of the trial

43.3 The Generalized Clinical Trial Cycle/ Process

Addressing all aspects of a clinical trial in depth is an enormous undertaking and beyond the scope of this chapter; thus, the following sections will highlight some of the foundational methods and processes of a typical heart valve clinical trial which can generally be translated to the complexities of other cardiac devices. As you can see in Table 43.2, there are many tasks that need to be addressed with the development and execution of a clinical trial. It is important to note that some of these tasks may occur simultaneously.

43.3.1 Features of a Trial Design for a Newly Developed Cardiac Device

It is pertinent to research and understand all current published information and relevant heart valve trial data prior to planning and executing a clinical trial. There is much to be gained from studying the details of previous trial designs, as well as the subsequent outcomes associated with those trials. In regards to gaining FDA approval for any cardiac device, the importance of clinical evidence cannot be stressed enough. In the beginning stages of planning a clinical trial design, associated publications and previous research may help shape important components for the new trial, such as: patient inclusion/exclusion criteria, statistical designs employed in such trials, and/or the general patient populations to be studied.

Table 43.2 Standardized clinical research process

1.	Prepare a clinical plan
2.	Recruit investigators
3.	Prepare protocol
4.	Prepare case report forms
5.	Prepare informed consent form
6.	Perform investigator site visit
7.	One-on-one investigator reviews, including clinical plan, protocol, case report forms, and informed consent form
8.	Obtain an investigator agreement
9.	Obtain IRB approvals for each participating institution
10.	File an IDE
11.	Obtain IDE approval
12.	Perform periodic investigator meetings
13.	Conduct the clinical study, i.e., a multicenter study
14.	Monitor the multicenter study
15.	Conclude study
16.	Compile data from each institution
17.	Analyze overall collected data
18.	Write final clinical report

A well-controlled clinical investigation includes a clear objective and defined methods of analysis. More specifically, the objectives should address the proposed medical claims for the investigational device and these objectives should be refined to explicitly address the safety and efficacy of the heart valve in a defined population. Next, it is important to structure a trial so there can be a valid comparison to controls. For example, in current transcatheter valve therapy trials, the new therapy (transcatheter valves) is directly compared to a standard open-heart valve surgery. A control group gives the results a meaningful comparison to an existing therapy or treatment, which is important to the scientific community and may be crucial for future marketing. Often, an appropriate control group can be identified by performing a careful and thorough literature search or seeking out the key opinion leaders in the related field. Furthermore, performing early research on the specific disease or conditions that the heart valve will treat is equally important, in order to understand the natural progression of the disease or condition and the current benefits or limitations of other treatments. It should be noted this step is often completed in earlier phases of device prototyping, but it is recommended that designers review the research once again just prior to planning the clinical trial. Finally, literature searches on similar treatments/heart valves can also assist in identifying the appropriate disease populations and justifying the inclusion and exclusion criteria for the trial.

When the patient population and treatment/control cohorts are clearly identified, one needs to consider the next set of factors that impact the ultimate design. First, the type of trial design must be determined, whether it is randomized, blinded, or double blinded. Each of the designs may strengthen the significance of the trial results, while also minimizing bias and providing comparability of groups. Well-defined trial endpoints are of great significance for the overall success of a clinical trial. For example, typical heart valve trial endpoints should encompass both safety and efficacy measures. Note that adverse events often comprise the safety endpoint for a given trial. Typically, effectiveness endpoints are found in the form of the presence or absence of a clear, definite effect on a patient, e.g., death or the resultant effective orifice area (EOA). Table 43.3 provides a list of key steps to consider in designing a clinical trial for the development of a new heart valve technology.

An often overlooked aspect of the early execution or startup of a clinical trial is a high degree of physician involvement or engagement. While physicians play a major role throughout the execution of the trial, it is important to gain physician insights into the overall design and planning of a clinical trial early on in the process. Being that physicians are ultimately the users of the heart valve being studied, their clinical knowledge can be valuable in creating a well-designed and thorough clinical trial.

43.3.2 Reimbursement and Payer Information

While the process for development of clinical trials is essential to understanding the appropriate use of medical interventions of all types, it is also important for payers to understand potential coverage for the device. When designing a clinical trial, it is recommended that one reads the National Coverage Determination for Routine Costs in Clinical Trials (310.1) provided by Centers for Medicare and Medicaid Services [6].

Table 43.3 General steps in the development of a clinical study design

• Develop study objective which includes research objective, device claims, and pilot of feasibility study
– Note that the study objective should be phrased as a research question posed to address medical claims for the device – Refine the research question to specifically address the safety/effectiveness of the device in a well-defined patient population for one or more outcomes – Perform a pilot or feasibility study; if claims are inadequately known, conduct a pilot or feasibility study on a small subgroup of patients or subjects. As such, the pilot study objectives are to identify claims more precisely, test study procedures, and/or obtain estimates of properties of outcome and/or other variables
• Properly identify and select variables/parameters • Define study population(s) and appropriate clinical controls
– Prior to study, define rigorous inclusion/exclusion criteria – Define subset of the general population representing the target population for the device
• List all parameters of the specific study design • Define study masking (i.e., your bias control) • Define number of study sites and potential investigators
– Fit the needs for a sufficient number of eligible patients in a timely fashion – Center must be capable of processing patients – Engage competent staff members who work well on the trial – Identify investigators willing to recruit patients and conduct the study as specified in the protocol – All center individuals need be qualified to perform trial parameters
• Determine proper patient sample size, i.e., the study is properly statistically powered

43.3.3 Clinical Trial Site Selection

By definition, investigational sites include all centers implanting the cardiac device that submit data as part of the investigation. The initial selection of the proper hospitals/institutions and physicians to participate in a given clinical trial is a crucial step toward executing a successful clinical research trial. After time and money are invested in creating the trial design and protocol, the actual execution can affect the outcome of the trial. Therefore, all possible steps should be taken to eliminate extraneous variables such as reeducation or elimination of a site that does not abide by the set protocol. Furthermore, the selection of appropriate physicians to participate in a clinical research trial is another variable to carefully examine before proceeding with the trial. It is critical to qualify the experience of the physicians relative to their ability to utilize novel or investigational therapies similar to the device you are investigating. It would be strategic to identify and recruit physicians already well established in the related therapy or device and those that are familiar with conducting complex clinical trials. These physicians will become the trial investigators responsible for the precise execution of the protocol at each institution or site. Not only should the physician investigators have adequate experience with clinical trials, but it is important to ensure that the institution's support staff is knowledgeable and skilled in their execution as well. It is good practice to check the institution's previous clinical trial performance. Finally, it is essential to make sure the physician investigators have not been disbarred, banned, or excluded from participating in any type of clinical trial.

Another pertinent variable to consider when selecting sites is the actual geographic location. The clinical trial design and projected subject population(s) are helpful when identifying the amount of sites needed in the trial. As such, typically large metropolitan area hospitals are chosen to participate in clinical trials from the perspective that they should be able to quickly recruit the desired patients. However, there are regional hospitals that receive a high amount of referrals; thus, these hospitals may be able to effectively contribute to enrollment in clinical trials. Ensuring that an investigational site has an adequate potential patient population is important, given the amount of time it takes to train the personnel at a site and activate them as a part of the trial. It is interesting to note that a very small percentage of American senior citizens participate in clinical trials, although the elderly bear a disproportionate burden of disease in the United States [7]. Sites that have experience working with and successfully recruiting the appropriate patient populations can be immensely helpful in enrolling subjects in a timely manner to complete a trial.

The potential for conflicts of interest is also something to manage when choosing clinical sites for a trial. More specifically, cardiac device clinical trials typically involve a high level of physician engagement in the trial and the technology/therapy being tested. Therefore, to legitimize their participation, it is critical to rule out any potential bias with regard to how the trial is run and the quality of the data being captured. It should be noted that many sponsors and clinical sites have built-in regulations or processes to cover any potential conflicts of interest.

43.3.4 Clinical Trial Execution

Throughout the execution of a clinical trial, there are multiple activities happening simultaneously that need to be managed (also dependent on design of the trial). For example, most subjects in the trial will require follow-up visits. Specifically for heart valve trials, it is important to design a trial with multiple follow-up visits in order to capture long-term data on the subject population(s). With clinical evidence being the primary end product of a clinical trial, it is crucial to ensure that institutions capture valid and accurate data in a highly efficient manner. Recently, there have been several technological advances to make capturing trial data more efficient and user-friendly for the hospital/sites. The trial data is captured on what most clinical trial sponsors called *case report forms*. Historically, the hospitals/sites would complete hard copy forms and send them back to sponsor(s); this could be quite cumbersome especially with monitoring and processing the data to ensure accuracy. Currently, nearly all trial data are collected electronically (sites enter data directly into an online case report form, and the sponsor can see the data in real time). Therefore, as new trials are rolled out and more heart valves are being studied, it will be critical to keep up with the ever-evolving technologies that are being developed and deployed to ensure the integrity, quality, and efficiency of clinical trials.

An interesting trend in recent transcatheter heart valve trials is the development and utilization of screening committees. For example, a screening committee for a heart valve transcatheter trial would typically be compromised of well-established, objective cardiac surgeons and interventional cardiologists. As such, it is imperative that these individuals also be familiar with the details of heart valve technologies and the trial design. Furthermore, it is important that the screening committee be knowledgeable about the patient population which the trial is enrolling as well as the specific inclusion/exclusion criteria. The screening committee could also be used to assist in determining and identifying the appropriate patients for a properly designed trial. It is critical to recruit an overall subject population that is highly consistent; this is especially important when multiple clinical sites/hospitals are participating in the trial.

Assuming the trial has progressed to the point of near completion, there are several other factors to consider.

For example, all subjects should be accounted for in the final clinical report. It is recommended that complete subject accounting, on a per subject basis, for each cohort is provided. Therefore, the report should include: (1) the total number of subjects expected for follow-up, (2) number of subjects discontinued because of death or device removal, and (3) number of subjects that were actually evaluated at each preplanned time point.

Depending on the type of trial and the primary endpoints listed in the protocol, submitting for regulatory approval may happen before the trial is fully complete. For example, in an IDE study with primary endpoints at 1 year of subject follow-up, an application for PMA may be submitted and granted prior to the end of all subject follow-up. Nevertheless, this will depend on the accepted trial design. It should be noted that the FDA expects long-term data for most IDE heart valve trials. Therefore, in some trials, the specific heart valve may be commercialized prior to the end of all follow-up visits, but regular reports continue to be submitted to regulatory bodies containing the long-term data. Finally, the overall timeline for submission for regulatory approval will ultimately depend on the statistical methods and analytical processes laid out in the final trial protocol. It is important that this section of the device trial protocol be carefully followed, as it is agreed upon by the FDA or regulatory body prior to initiation.

Excerpts from the Draft Guidance for Industry and FDA Staff Heart Valves—IDE and PMA Applications are outlined below to provide clear direction from FDA's perspective on the conduct of a heart valve clinical trial [2]. Again, it is important to reference the appropriate FDA guidance that your cardiac device may fall under.

43.3.5 Data Collection Within the Clinical Trial

As clinical evidence to support the use of the investigative heart valve is the ultimate product of conducting a clinical trial, the remainder of this chapter will focus on the collection of data and various regulations one needs to consider related to clinical evidence. FDA guidance provides detailed insight into what is expected in a data collection plan and therefore should be referenced frequently throughout development of the protocol. Listed below is an important narrative from the FDA Guidance document that one should understand prior to data collection:

> The sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, requirements in 21 CFR Part 812 or other applicable FDA regulations, or any conditions of approval imposed by the reviewing investigational review board or FDA is responsible for promptly securing the investigators compliance or discontinuing shipment of the device to the investigator and terminating the investigator's participation in the investigation (21 CFR 812.46(a)). Your protocol must ensure that the investigation is scientifically sound by ensuring consistency between the indication studied and the subject inclusion and exclusion criteria (21 CFR 812.25(b)). In all study designs, you should ensure that investigators collect the appropriate information. Specifically, you should ensure that the clinical data collection forms used by the investigators and institutions are consistent with the clinical protocol. You should also ensure that informed consent document(s) is consistent with the clinical protocol [2].

43.3.6 Data Collected for Each Subject Enrolled into a Clinical Trial

Each subject enrolled in the study should be followed and appropriate data collected according to the study protocol. Additionally, follow-up data should be collected for each subject until the entire study is terminated for all subjects; this follow-up data is typically collected during office, clinic, or hospital visits. It is recommended that telephone follow-up should be used only to verify death or loss to follow-up. Being data should be collected until the entire study is terminated for all patients, the follow-up period may be significantly longer than stated in the original study protocol for most patients. Accordingly, an informed consent must be received for the planned follow-up period from all subjects (21 CFR 50.25(a)(1)). Therefore, any subject not willing to fully participate in the study, which includes the follow-up period, should not be enrolled [2]. Most institutions have a thorough consent process, as governed by regulatory bodies and their own IRBs. This consenting process will ensure that subjects being enrolled in the trial will complete all follow-up visits; however, trial attrition still occurs. There is the potential that some patients will enroll in a clinical trial to obtain the latest technologies, with little or no intent of being part of post-monitoring.

The FDA's guidance goes into more detail about the specific data they would like to see collected, as it will help ensure consistency across populations receiving heart valves (Table 43.4). For example, follow-up data for most heart valve trials should include the normal ranges for the clinical laboratory blood tests evaluated, according to the normal

Table 43.4 Echocardiographic hemodynamic data (stratified by valve size for each patient enrolled)

• Peak pressure gradients
• Mean pressure gradients
• Effective orifice areas
• Existence and/or relative degree of valvular regurgitation
• Native valve's effective orifice area index
• Native valve's performance index
• Resting cardiac output
• Average cardiac index

ranges used by the laboratories that conduct the testing. Plasma free hemoglobin is preferable to serum lactate dehydrogenase, haptoglobin, and reticulocyte count for the evaluation for hemolysis because it is considered that plasma free hemoglobin has higher clinical sensitivity for the detection of hemolysis than the other three laboratory tests. The diagnostic preoperative data collected should include the normal ranges for the clinical laboratory blood tests that are evaluated, with the normal ranges being determined by the laboratories used [2]. As detailed, it should be apparent the amount of data and work institutions will undertake to participate in new heart valve trials.

Typically, enrolled patients will be followed subsequent to the procedure by their personal cardiologists (not the implant surgeon/interventionalist), and often there will be preclinical data available for a given patient as well. Therefore, the study investigators should work in conjunction with the patients' physicians to collect all appropriate data from the correct time periods. This may be better accomplished if the study investigator or the sponsor obtains contact information for the following physician, so he/she can be advised of the actual study protocol. It is important to note that only study procedures (out of the standard of care scope) should be performed by investigators trained on the trial protocol.

As there is increasing interest in all valve positions, FDA guidance has started to address specific details for these different positions. It is recommended for trials that involve replacement of pulmonic valves and/or pulmonic-valved conduits that one should calculate the effective valve orifice area, since the cone shape of the right ventricular outflow tract makes echocardiographic measurements of the right ventricular outflow tract diameters very difficult. This measurement, if identified within a clinical design, may lead to potentially inaccurate calculations, i.e., if one employs a continuity equation method for the pulmonic valve EOA. Similarly, for replacement pulmonic valves and pulmonic-valved conduits, the FDA does not recommend calculation of EOA indexes and performance index data, which are determined using EOA data [2].

43.3.7 Clinical Trial Follow-Ups

In general, each subject entered into the study should be followed and appropriate data collected according to the study protocol, and associated follow-up data should be collected for *each* subject until the *entire* study is terminated for *all* subjects. Unfortunately, this is not always the case; therefore, it is important to plan for potential attrition in the statistical plan by having an adequate population enrolled greater than the minimum number of patients needed for an appropriate analysis. It is helpful to determine the appropriate subject population by referring to the term *follow-up in patient-years*. For example, the recommended follow-up of 800 patient-years is statistically derived as follows. Single sample one-sided hypothesis testing can be used to demonstrate that each of the complication rates associated with the investigational device is less than 2 times the objective performance criteria (OPC) for that complication. The appropriate null hypothesis is that the true rate associated with the investigational device is 2 or more times its OPC. To reject this null hypothesis is to accept the alternative hypothesis that the true rate associated with the investigational device is less than 2 times its OPC [2].

Generally, in order to provide a clinically sufficient amount of data on the investigational heart valve technology, it is generally recommended by the FDA that all subjects be followed for 1 year or more. If a clinical investigation is for one valve position, it is recommended that at least 300 subjects are followed for 1 year or more, for a total of 800 patient-years of follow-up. If the study is for two valve positions (i.e., aortic and mitral), it is recommended that at least 150 subjects are followed for 1 year or more for each valve position, for a total of 400 patient-years of follow-up per valve position. It is generally recommended that one conducts a valve technology clinical study at eight or more primary centers, with 30+ subjects implanted at each center for a one-position study and 15+ subjects implanted at each center for a two-position study [2]. As noted within the FDA recommendations, using fewer than eight primary centers can introduce unanticipated bias into these complex clinical trials.

Some heart valve technologies may be implanted or deployed in more than one of the four heart valves. Therefore, it has been specifically recommended by the FDA that, for one-position and two-position studies, trials be designed for the subsequent implanting of 15+ subjects for each size and each position of valve. In other words, if a study assesses the potential for both aortic and mitral replacement with a given technology, the study should enroll 15+ subjects at the aortic position and an additional 15+ subjects at the mitral position, for each valve size. It should be noted that this recommendation of 15 subjects implanted per size per position criterion is based on statistical calculations for echocardiographic EOA data; these calculations showed that in order to assure a sufficiently narrow 95 % confidence interval, the minimum number of subjects implanted with each valve size was 15. If you were to design a trial in which you hoped to omit any valve size, the FDA specifically recommends that you explain how the data you plan to collect would still remain representative of all the sizes that you intend to market. With the rapid development of cardiac imaging capabilities, any well-designed clinical trial on a valve technology will also require follow-up image assessments (Table 43.5).

43.3.8 Complications and Complication Rates

The types of complications to expect from patients treated with newly developed valve technologies include valve thrombosis, major hemorrhage, perivalvular leak, and/or stroke. For the initial three complications, the rate of occurrence with current technologies is typically less than 1.2 % per patient-year (i.e., within 800 patient-years) for aortic and mitral positions combined [2]. Therefore, such rates typically must be matched or exceeded by the novel technology. It is generally recommended for valve technologies that the complication data include hemorrhages resulting from all causes (all-cause hemorrhage) rather than just hemorrhages related to anticoagulant therapy (anticoagulant-related hemorrhage). Additionally, it is typical that the complication data include all-cause reoperations, valve-related reoperations, explants, all-cause deaths, and valve-related deaths.

The clinical trial sponsors are ultimately responsible for ensuring proper monitoring of the investigation and must select non-biased monitors qualified by appropriate training and experience. For example, the FDA generally suggests that each trial sponsor (designer) establishes a Data Safety Monitoring Board (DSMB) to review adverse events and recommend study termination if safety concerns are warranted. Nevertheless, the DSMB should establish criteria for recommending study termination for safety reasons before the study begins and should meet at least two times during the study to monitor adverse events. Furthermore, it is recommended that the DSMB should include members who are independent from the study sponsors and investigators; additionally, two or more members should be physicians including a cardiothoracic surgeon and a cardiologist. Additionally, if the study involves statistical analyses, one member should be a qualified statistician.

It is also recommended that the sponsor establish a Clinical Events Committee (CEC) in order to adjudicate adverse events as being valve technology related or not and to classify the severity of an elicited adverse event. Similar to the DSMB, the CEC should have members who are independent from the study sponsors as well as selected clinical investigators. It is important to charter CEC and DSMB committees for a trial, as they add independent validation to the credibility of the research. As the execution of the study proceeds and endpoints are reached, the CEC and DSMB committees will be commissioned to adjudicate the data which will be necessary for the PMA submission. Table 43.6 outlines the recommendations for what should be included in a PMA submission.

A PMA should include the actual number of all noted adverse events. In addition, it is generally recommended that

Table 43.5 Reports included as follow-up data

• Echocardiograms
• Cardiac catheterizations
• Other cardiovascular imaging procedures, including CT and MR scans
• Chest X-rays

Table 43.6 FDA recommendations for a final premarket approval report

• Summary of patients/subjects not completing the study (stratified by lost to follow-up, death, or explant)
• Specific locations of all investigational sites in which procedures were performed
• Relative comparison of preoperative and postoperative NYHA functional class (presented as the percentage of subjects in each class at baseline, at each follow-up time point, and as the percentage of subjects at each follow-up time point who improved, worsened, or did not change in class)
• Pre-implant/procedure effective orifice area of the given heart valve
• Number of implanted patients/subjects stratified by the given investigational sites, replacement/repair valve positions (e.g., aortic, mitral, or double valve), and/or employed valve sizes
• Number of treated patients/subjects followed to 1 year post-procedure, stratified by investigational site, valve treated (e.g., aortic, mitral, or double valve), and/or employed valve sizes
• Follow-up duration information (total and by valve position) including mean follow-up times, standard deviations, range of follow-up, and cumulative follow-up in patient-years
• Any identified confounding factors (e.g., by hazard regression analysis applied to identify risk factors, gender, age at implant, preoperative NYHA functional classification, previous valve surgery, concomitant coronary artery bypass surgery, implant position, and implant size) which might affect the incidence of reoperation, explant, and/or death
• Patient compliance data for follow-up visits (e.g., NYHA functional classification data, echocardiographic data, and/or clinical laboratory results)
• Complete list of complications by patient identification number
• Summary of any and all subject complaints received
• All case report forms (i.e., for a 10 % random sampling of the subject population)
• All copies of case report forms for each and every subject not completing the study
• Explant analysis data obtained for each and every case (i.e., when a valve was explanted or an autopsy was performed)
• All death reports, including autopsy reports when available, especially when the cause of death was classified as non-valve related

the trial sponsor expresses early complication rates as the number of adverse events divided by the total number of subjects [2]. A sponsor should also include linearized late complication rates; these rates are calculated as the number of late adverse events divided by the total number of late patient-years.

With the rapidly changing regulatory environment and concerns for ensuring safety of cardiac valves, the clinical trial process will continually evolve. It is important to keep up to date on additional requirements and landmark trials that are testing devices similar to the new heart valves being developed today. The FDA provides valuable resources on their website along with a repository for most clinical trials that are occurring in the United States (www.clinicaltrials.gov).

43.4 Summary

Clinical trials are an important and critical step in bringing new technologies, such as cardiac devices, to the market. As detailed above, there are many facets involved in the development and execution of a clinical trial. This chapter provides a high-level overview of these aspects, which may vary from product to product. Setting up a calculated trial and executing it proficiently will affect the ability to successfully market a cardiac device. The clinical trial requirements and regulatory and reimbursement landscape are vast and constantly changing. When designing a clinical trial, it is important to keep in mind the various regulatory requirements, the importance of GCP, the selection of participating institutions, data collection, endpoints, and overall execution of the trial. With such a heavily regulated environment as well as the intricacies of cardiac devices, ensuring proper conduct to ensure high quality data is crucial. This chapter provides a general overview of the present state of human heart valve clinical trials, including: (1) the current positions of regulatory bodies that oversee trials, (2) specific features of a trial design, and (3) considerations involved in the proper implementation of trials.

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