Chapter 22
Regulatory Issues

The purpose of a clinical trial is to assess reliably the benefits and harms of an intervention. In this book, we have focused on good clinical trial design, conduct, monitoring, and analysis principles. For many clinical trials, including those involving new drugs, devices, or biologics, or new indications for existing interventions, there are national and local regulations that must be followed in order to conduct clinical research, including the types of trials we have discussed. Furthermore, in order for an industry sponsor to market a medical product, regulatory agency approval is required in the U.S. and much of the rest of the world. The primary goal of this chapter is not to summarize all of the regulations relating to medical products; that is beyond the scope of this book. Rather, it is to focus on those laws, regulations and policies that bear on the design, conduct, and reporting of clinical trials. Even then, it will be highly selective, limited to those aspects that we think are most relevant and we will concentrate on U.S. laws, policies and regulations.

In the U.S., the Food and Drug Administration is the agency that reviews products for marketing and use to prevent disease, diagnose disease or treat individuals or animals, regardless whether the product was developed by industry or other research institutions. The FDA is a large organization composed of seven Centers: Center for Drug Evaluation & Research (CDER), Center for Devices & Radiological Health (CDRH), Center for Biologics Evaluation and Research (CBER), Center for Food Safety and Applied Nutrition, Center for Toxicological Research, Center for Veterinary Medicine and Center for Tobacco Products [1]. (See Fig. 22.1.) Most of these Centers have divisions that reflect disease types such as cardiovascular and renal diseases, or types of interventions such as cardiovascular devices or surgical devices. While each Center abides by the laws under which it was created and follows the regulations written to describe its standards and procedures, there are important differences in the kinds of study designs (control groups, end points, blinding, etc.) that reflect the specific disease area or product type.

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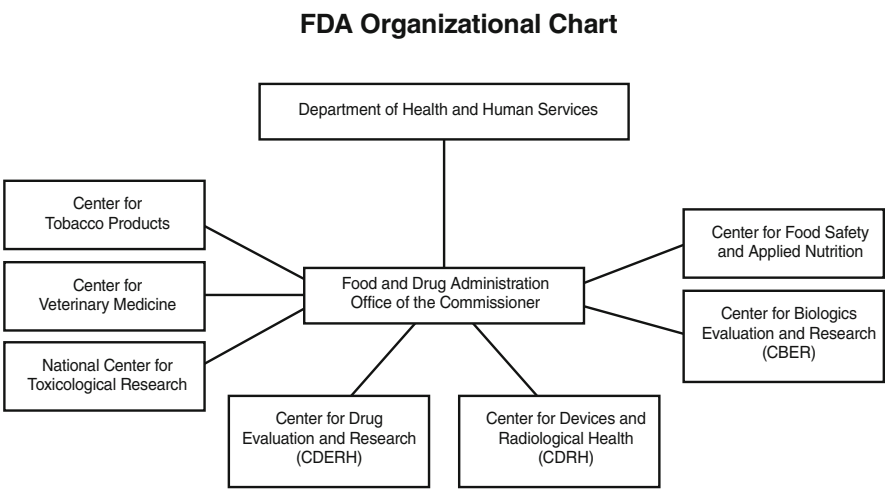

Fig. 22.1 FDA organizational chart 2013

In Europe, the European Medicines Agency (EMA) has regulations that apply to those countries under its purview [2]. The development of the International Conference on Harmonisation (ICH) guidance documents [3] was aimed to make clinical trial standards more comparable internationally. But regulatory agency rules and guidelines still differ among countries, and these differences may contribute to different approval decisions [4]. Regulations and guidelines in Europe have changed over time [5]. Importantly, rules of conduct differ in the various countries in which a multinational trial might be conducted. Even within a country with a common standard, differences in judgment in applying those standards may exist. Thus, another purpose of this chapter is to provide links and other sites to which investigators can go for fuller and more current information and assistance.

The differences can be challenging for a new investigator to navigate. Nevertheless, investigators must become knowledgeable if they want to develop a successful clinical trial program.

Fundamental Point

When designing and conducting a clinical trial, investigators must know and follow national, state, and institutional regulations that are designed to protect research integrity and participant safety.

Background

Overview

Research under the Code of Federal Regulations is defined as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" [6]. Clearly, clinical trials fall into that definition.

Clinical research regulations (or rules) and guidelines in the U.S. are created at the federal level by the Department of Health and Human Services, the Office of Human Research Protection and the Food and Drug Administration (FDA) and include several guidance documents [6–9]. In addition there are local requirements from universities and other research institutions, in response to some of the federal guidelines. Clinical researchers must be familiar and be in compliance with these regulations and guidances. Finally, the FDA requires investigators and trial sponsors to register all trials with ClinicalTrials.gov [10], providing basic information about the design of the trial within 21 days after the first participant is enrolled, and within 1 year after trial completion to submit the overall results to the same web site [11], as discussed below.

Other chapters in the book cover regulatory issues as they concern topics discussed in those chapters (Table 22.1). Chapter 1 discusses clinical trial phases. Chapter 2 contains discussions of trials in emergency settings and studies that enroll vulnerable populations, which have special regulatory requirements, as well as requirements for Institutional Review Boards that are mandated in the Code of Federal Regulations [6], sometimes referred to as the Common Rule. These will not be repeated here. Noninferiority trials, the use of adaptive designs, and cross-over trials, all of which might involve input from regulatory agencies, are discussed in Chap. 5. In this chapter, we will focus on pretrial requirements, trial conduct, and posttrial requirements.

History

Regulation of drugs, devices, and other medical products has a long history [12, 13]. In many countries, including the U.S., various laws and amendments require that new products (i.e., those not yet marketed) such as drugs, biologics or devices be proven safe and effective before they are approved for marketing. As medical practice and our understanding of how interventions work improves, and as a result of several egregious events [14], these regulations have evolved over the years. Following the Pure Food and Drug Act of 1906, a key event in the U.S. was the passage of the Food, Drug, and Cosmetic Act of 1938 [15]. Among other things, this act required that new drugs be shown safe and authorized standards of quality. In 1962, the Kefauver-Harris Drug Amendments required that the effectiveness of products be shown before marketing [16]. They said that the required "substantial

Table 22.1 List of regulatory issues discussed in other chapters

		Pages
Chapter 1	Trial Phases	4–10
Chapter 2	Ethics Committees	25, 28–29, 31–34, 36, 39
	Informed Consent	34–37, Table 2.2
	Trials in Emergency Settings	36
	Trials in Vulnerable Populations	37
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Chapter 5	Cross-Over Trials	102–103
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	Boxed Warnings and Drug Approval Withdrawal	258
	Classification of Adverse Events	260
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Chapter 13	Health Related Quality of Life/Patient-Reported Outcomes	279
Chapter 16	Data Monitoring Committees	345–350, 367
Chapter 19	Data Cleanup and Verification	469
	Storage of Data and Materials	470–471
Chapter 20	Data Sharing	493–494
Chapter 21	Globalization of Trials	511–514
	Site Investigator Responsibilities	510, Table 21.1

evidence" of effectiveness could be demonstrated only on the basis of "adequate and well-controlled trials." The "s" at the end of "trials" is important as it implies that more than one trial is needed. The Medical Device Amendment in 1976 provided guidance on how devices were classified for regulation and approval [17]. The Safe Medical Device Act (1990) further expanded the role of the FDA [18].

In recent years, there have been rules that allow for making drugs available as rapidly as possible, including four approaches: *fast track, breakthrough therapy, accelerated approval*, and *priority review* [19]. *Fast track* is aimed at expediting review of drugs filling unmet clinical needs for serious conditions. *Breakthrough therapy* is a process for drugs that have early evidence of improvement over available treatments for serious conditions. *Accelerated approval* is for unmet clinical needs for serious conditions using surrogate endpoints with a requirement for further studies. The *priority review* designation provides for an FDA goal of regulatory action within 6 months (compared to 10 months under standard review), based on anticipated significant improvements in safety and/or efficacy for serious conditions.

Regulatory Requirements

Table 22.2 lists key actions and responsibilities required of investigators (both lead and other) conducting trials that fall under the purview of the FDA.

Although the principal investigator (PI) is traditionally considered to be the individual designated as being responsible for the clinical trial, from a regulatory perspective, it is the sponsor who has primary responsibility. "The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator" [20]. Thus, being PI on a grant that funds the clinical trial is not the same as being a sponsor. The sponsor is responsible for seeing that all of the documentation, approvals, and reporting requirements, including under the purview of the IRB, are fulfilled. The same individual often serves in both capacities, but they need not be the same. As listed at the end of this chapter, many guidance documents are available on the web to help familiarize investigators beyond the level of detail presented here. The National Institutes of Health and many universities require clinical researchers to take courses or workshops (often online) on research ethics and regulations, and many research institutions provide them. See Chap. 2 for specific resources.

The U.S. Health Insurance Portability and Accountability Act (HIPAA), passed in 1996, includes the Privacy Rule that protects the privacy of individually identifiable health information [21]. The HIPAA Privacy Rule gives conditions under which protected health information (PHI) may be used or shared with individuals or what is referred to as covered entities for conducting medical research. Protected health information refers to patient names, date of birth or other identifying dates, telephone numbers, email addresses, Social Security numbers, medical record numbers, photographs or any other identifying information. The HIPAA establishes conditions under which PHI data collected for research may be used or disclosed for research purposes, including who may obtain such information. Trial participants must be informed of uses and any disclosures of their medical information and disclosure of PHI data requires the permission of the individual or special approval procedures. If clinical trial data are shared outside of the trial that collected the data, they must be de-identified [22]. These HIPAA requirements can bring challenges in carrying out clinical trials. The investigator is responsible for doing this correctly. Often, these issues can be addressed in the informed consent process if anticipated.

Trial Phases

Clinical trial phases are discussed in Chap. 1. It should be noted that traditionally it was the drug trials that were divided into phases I, II, III, and IV [23]. Guidelines for early phase studies for biologics have also been developed [24]. These take into account the special needs of development and testing of cellular and gene therapy products and other biologics.

Table 22.2 Actions and responsibilities of investigators conducting clinical trials under auspices of FDA

	Trial	Site
	Leadership	Investigators
Pretrial		
Ethics Training		
Principles of Research	x	x
IRB Requirements	x	x
Informed Consent Process	x	x
Knowledge of Basic Regulations		
45 CFR 46 (Common Rule)	x	x
21 CFR 50 (FDA Regulations)	x	x
45 CFR 160 (Privacy Act)	x	x
IND or IDE Completion		
Pre-clinical materials and references	x	
Final protocol (allowing FDA up to 30 days for review)	x	
Information Showing Competence of Investigator(s)	x	x
Information Showing Adequacy of Facilities	x	x
Registration with ClinicalTrials.gov	x	
IRB Approval	x	x
Conduct		
Site Monitoring	x	
Data Monitoring	x	
Other Quality Assurance Activities	x	
Reporting to IRB(s) and FDA		
Protocol Modifications	x	
Investigator Changes	x	
Safety Reports		
Serious Adverse Events	x	x
Routine	x	
Posttrial		
Submission of data and documents to FDA (if seeking product approval)		
Protocol	x	
Completed Case Report Forms	x	
SAE Reports	x	
Product Accountability	x	
Presentation to Advisory Committee	x	
Possible Conduct of Post-Approval Studies	x	x
Publication of Trial Results	x	x
Timely Submission of Data to ClinicalTrials.gov	x	

Before marketing of a new product or for a new indication of an already approved product, late phase trials are typically conducted. Sometimes, though, new products or new indications may be approved on the basis of trials that do not use clinical outcomes but rather an intermediate outcome as a surrogate endpoint With devices, the situation is even more variable, as modifications of approved devices (through the 510 (k) process [25]) may not require any clinical trials when a suitable combination of preclinical data (i.e., bench testing, animal model, and computational modeling) can be demonstrated to show substantial equivalence to the predicate device.

Pretrial Requirements

What kinds of trials do and do not require regulatory agency approval? Trials that involve new drugs, devices, and biologics that are not marketed require approval prior to conduct. Interventions that are already approved for the indication that is being studied in the trial do not generally need to be submitted for FDA regulatory review. For example, a drug may have been approved on the basis of a surrogate outcome, but an investigator now wants to evaluate it using a clinical outcome. Though, if the trial is to test a new indication or to evaluate the intervention administered in a different way or using a different dose, regulatory agency approval would typically be required [26, 27]. If new information is to be generated with the intent of including that information in the drug label or in advertising, an Investigational New Drug Application (IND) is needed [28]. Non-drug and non-device trials, where the intervention might consist of training, education, or surgical procedures do not, as a rule, require prior approval by the FDA, although other countries may require national regulatory approval even for these trials.

The FDA and the EMA websites include current clinical trials guidance documents, as well as forms that need to be completed for trials of drugs or biologics and devices [2, 9]. All investigators considering conducting clinical trials that might fall under FDA or EMA guidance should consult these materials before designing the trial. The version of the ICH document E6 (Good Clinical Practice: Consolidated Guidance) [29] that was amended in June, 2014 contains considerable information concerning the design and conduct of clinical trials and is generally consistent with the fundamental principles outlined in this book. While this document was created with a focus on all phases of pharmaceutical trials, and it has features that are overly complex for many large, simple or pragmatic trials, it does allow for some flexibility [30].

In advance, it is often useful and recommended to meet with staff of regulatory agencies to discuss the planned protocol and the proposed data to be collected, especially for phase III studies. This is especially true in an area where scientific knowledge is rapidly changing or if other than a standard design and outcomes are being considered. For example, if any of the adaptive designs will be used (see Chap. 5), it may be advisable to solicit advice from the FDA. Similarly, if the

outcomes that will be used are not ones that are generally accepted for the condition being studied, discussions with regulatory agency staff are essential. The FDA may agree that some of the proposed data collection is not necessary for their approval process and offers an opportunity for some reduction in effort and cost. Additionally, studies in children or other vulnerable populations, and trials in emergency settings have special regulations and requirements of which investigators need to be aware.

The draft protocol and the statistical analysis plan along with the data monitoring charter and the monitoring plan, if appropriate, should be submitted to agencies before the trial begins. For complicated Bayesian or adaptive designs the actual computer code may be requested by a regulatory agency to independently assess accuracy.

Conduct

Protocol amendments for a trial being conducted under an Investigative New Drug (IND) application should be submitted prior to implementation. Also, after initiation of the trial, investigators and/or sponsors must report adverse events to the regulatory agencies. Generally, this is as an annual report. However, serious adverse events, particularly those that are unexpected or life-threatening, need to be reported in a more prompt manner. For FDA definitions of serious, life-threatening, and unexpected, and what actions need to be taken, see Chap. 12. As a rule, those that are unexpected (e.g., not related to the condition being studied nor in the drug investigator brochure or the package insert) need to be submitted in a timely way as safety reports. Historically, investigators reported to the trial sponsor any and all adverse events they discovered with the trial participant, and in turn these reports were sent to the FDA and other regulatory agencies as well as to all investigators in the trial worldwide, who in turn, sent them to their ethics committees. This resulted in a flood of individual adverse event reports that by themselves were largely uninterpretable. It has been recognized that this extensive adverse event reporting is not only unhelpful, but can be harmful to trial quality, since it diverts limited resources from aspects of trial conduct that are more important for quality.

As a result, in 2011 the FDA issued a new Investigative New Drug (IND) Rule for drugs that tried to reduce the number of adverse event reports that were not informative [31]. In the revision, the sponsor of the trial is to review the investigator reported events and determine if these events are Serious Unexpected Suspected Adverse Reactions (SUSARs) before they are reported to the FDA. Serious adverse events (SAEs), defined as events that are fatal, life threatening, require hospitalization, or result in permanent injury, must be reported in a more expedited fashion (e.g., less than 15 days from identification). Unexpected refers to events that are not listed in the Investigator Brochure or the package insert or other relevant documents regarding the product. A suspected adverse reaction is an event that has a

reasonable probability of being caused by the intervention and is otherwise uncommon in the treated population. An event may be a SUSAR if it is: 1) a single occurrence of an uncommon serious adverse event that very rarely occurs spontaneously (e.g., Stevens-Johnson syndrome), 2) one or more occurrences of event that does not commonly occur (e.g., tendon rupture), or 3) an aggregate analysis of a specific event in a clinical trial observed more frequently on drug than control [31]. Implementing this new IND rule has been challenging because sponsors have been reluctant to unblind even small numbers of participants with these SAEs while the FDA has said that the needed assessment will generally require unblinding of certain parties within the sponsor organization in a way that will not damage the study integrity [32]. Those parties who are unblinded should not be those involved in the conduct of the trial and they should not be investigators.

It may not be necessary to collect adverse events that are non-serious and that do not result in discontinuation of study drug after data have been collected on a certain number of participants(e.g., 2,000 to 5,000). Whether to collect all adverse events for a non-approved drug needs to be negotiated with the FDA before the trial begins. Serious but expected adverse events (related to the drug and/or expected in the course of the disease) may be collected on the case report form, and reported to the FDA in a systematic way, again with prior agreement of the agency.

A certain amount of quality assurance by the study sponsor is essential (see Chap. 11). Obviously, those that ensure proper assignment to intervention and control (including the randomization process), appropriate intervention, and outcome assessment are important, as are those that guarantee ethical standards (e.g., informed consent). Ongoing measurement, feedback, and improvement of these parameters are necessary during the conduct of the trial. Corrective action can be taken so as to prevent continuation of data collection problems and poor application of the protocol. Source data verification of all variables, and using this information simply at the end of the trial for documentation, is usually not helpful because the trial is over and it is too late to take corrective action. However, regulatory agencies reserve the authority to check on data that have been collected, including by means of visits to clinic sites. Investigators should be prepared for such visits, particularly at the end of trials that are viewed as yielding practice-changing outcomes. These visits may also review documentation of informed consent and study drug reconciliation, accounting for the amount of drug received and the amount dispensed according to the protocol. Standards for computerized data systems and record retention are included in guidance documents [33]. It should be emphasized that site visits may be of three sorts; routine, structured, and for cause. See Chap. 11 for a discussion of the kinds of audits.

Often, however, the effort spent on quality assurance is beyond what is needed for important aspects of trial quality and required by regulatory agencies [34–37]. Having unbiased assessment of key primary outcomes without an unusually large percentage of missing data will do far more to promote good quality clinical research than spending time and resources ensuring that secondary and tertiary measures are perfectly performed. Additionally, site visits to clinics for data verification are often unnecessary, as most key monitoring can be done centrally.

There may be other reasons for site visits, though. For example, they help to assure appropriate training of research personnel and adequate understanding of the protocol and the informed consent process. Regulatory agencies have given mixed messages regarding the kinds and amount of essential quality assurance. Therefore, many clinical trial sponsors, especially those from pharmaceutical and device companies, have typically engaged in exhaustive quality assurance. Yet the results of many trials conducted by others (e.g., the National Institutes of Health) have been accepted by regulatory agencies despite less extensive quality assurance. Central and "risk based" monitoring is within the FDA guidelines [38] and should be actively discussed with the agency in early phase meetings to determine if appropriate.

The U.S. law requires that clinical trials conducted in emergency settings, when informed consent is unobtainable, have a data monitoring committee [39, 40]. With that one exception, data monitoring committees are not required by law. FDA guidelines, however, discuss the importance of an independent data monitoring committee when the trial outcomes entail mortality or major morbidity, when there are major risks to the participants, or when having such a committee will "help assure the scientific validity of the trial" [40]. There is considerable emphasis on the independence of the committee members and on keeping the trial sponsor uninformed of interim data by intervention assignment. The European Medicines Agency has issued similar guidelines [41]. The International Conference on Harmonisation (ICH) [42] and the World Health Organization [43] also provide guidelines that are generally consistent with those of the FDA. For a fuller discussion of regulatory guidelines and data monitoring committees, see Chap. 16, and Ellenberg, Fleming, DeMets [44].

Interventions: Drugs

The classic structure of clinical trials, with its phases, placebo control, and blinding, derive from trials of drugs. Most regulatory agencies require that new drugs or drugs being tested in new settings or for new indications undergo the kind of clinical trials described in this book. Obviously, depending on the situation, the comparison may be another drug already proven to be beneficial or accepted as standard therapy, rather than placebo (unless the placebo is on top of standard therapy), and the trial could be designed either as a superiority study or as a noninferiority trial. In some circumstances (see Chap. 5), crossover or other special designs might be used.

Approval of drugs generally falls into the responsibility of the FDA's Center for Drug Evaluation and Research, better known as CDER. (This is somewhat of an oversimplification since some biologics can be viewed as drugs but are reviewed by the Center for Biologics Evaluation and Research.) Within CDER, there are many Divisions to handle drugs for different disease entities. Divisions may use external advisory committees to assist them in their evaluations. Criteria provided in the FDA and ICH guidelines are applied in the approval process for level of evidence.

Prior to initiating the evaluation of a new drug in humans, an Investigational New Drug (IND) application must be submitted [26]. One basis for this requirement is the federal law that requires such submission before a drug can be transported across state lines for research purposes. During early phase pre-clinical development, sponsor and investigators are attempting to establish some evidence of favorable drug activity and that it is reasonably safe to administer to humans for initial testing [23]. This generally means that the molecule has been screened for pharmacologic activity and toxicity in animal models. As the drug development progresses under the IND through the various phases, typically including two phase III trials, sponsors will submit all of their data as part of a New Drug Application (NDA) for approval for sale and marketing in the U.S.

Safety standards are not different for expedited review, accelerated approval or regular approval, but the efficacy requirements are different, as accelerated approval is based on an intermediate marker used as a surrogate outcome, with requirements for further studies using clinical outcomes. Post-market safety issues after approval of a drug that may later turn out to be not beneficial, or even harmful, can arise with any of the approval strategies. In 2012, the FDA approved the use of ponatinib for chronic myeloid leukemia, under an accelerated approval pathway, on the basis of hematologic and cytogentic reponses as the primary outcome [45]. Subsequently, increases in cardiovascular, cerebrovascular, and peripheral vascular thromboses were observed. This led the FDA to at first suspend, and then allow limited marketing of the drug. The FDA approved bedaquiline for drug-resistant tuberculosis on an accelerated basis for a serious unmet need using results from a trial showing greater conversion of sputum culture from positive to negative [46, 47]. This was done despite more deaths in the bedaquiline group than the placebo group (10 out of 79 vs. 2 out of 81), in part because of the urgent need for effective anti-tuberculosis drugs. A drug that seemed to clear sputum seems unlikely to increase death from tuberculosis and renders the patient noncontagious. The fact that many of the deaths did not seem to be drug related and occurred long after the patients were off treatment were also determining factors in the accelerated approval [48]. However, as with any accelerated approval based on a surrogate, the FDA required that a confirmatory trial be conducted.

Interventions: Devices

Approval of devices in the U.S. has usually not required the same kind of evidence as approval of drugs since regulations for device approval were developed separately and at different times [17, 18]. In many cases the mechanism of action and performance of a device can be adequately assessed without a large clinical trial. Examples might be diagnostic coronary catheters or electrocardiographic machines where proper preclinical bench testing is what is needed to assess adequate performance. On the other hand, with the burgeoning importance of device technology, well designed and performed clinical trials to assess safety and effectiveness may

be needed to properly assess devices. Recent examples include drug-eluting stents and percutaneous aortic valve devices. Device review and approval falls under the FDA's Center for Device and Radiological Health (or CDRH). Similar to CDER, CDRH has internal divisions based on disease or device type (e.g., cardiovascular devices or surgical devices) and also use external independent advisory committees to assist in the review and approval process.

Medical device development often has important differences from drug development. Drugs do not often change over time but devices are continually being changed (improved or modified) based on bench or clinical performance. With complex devices the performance of a device, and subsequent clinical results, may be operator dependent, which is not typically the case for drugs. Device development may be led by visualization of the performance of the device that is clearer than predicting the action and effects of a drug. FDA device laws and regulations traditionally required only one trial where drugs typically require a minimum of two trials although there is now some flexibility in that due to the 1997 FDA modernization act [49].

Unlike drug regulation which utilizes a reasonable uniform pathway for regulation, devices are classified into one of three categories or classes that affect the standards for approval and the approval process [50]. These classes are based on the level of control necessary to establish safety and effectiveness. Class I devices have minimal risk and are defined as those not intended to support or maintain life and may not present any risk (e.g., surgical gloves). Class II devices have moderate risk and are designed to perform as indicated without causing harm or injury (e.g., infusion pumps, diagnostic catheters, guidewires). Class III devices are high risk and generally support or sustain human life or present a potential for an unreasonable risk of illness or injury (e.g., pacemakers, defibrillators, heart valves). These devices require FDA approval of a premarket approval application (PMA) Due to the complexity of these devices, extensive preclinical and clinical testing are often required prior to approval, making this application process in many ways similar to the standard drug approval process [51]. A 510 (k) premarket notification [52] allows the FDA to evaluate whether the proposed device is essentially equivalent to a predicate device already cleared via a 510 (k). This might be the case for a modified model of the original predicate or a competitor's "equivalent" model. An investigative device exemption (IDE) is much like an IND for drugs in that it gives the manufacturer permission to conduct trials on the device, usually in preparation for a PMA submission [53, 54].

A PMA device is considered safe when, based on valid scientific evidence, the probable benefits outweigh the probable risks as long as the device is used according to conditions for which it was intended. A device is considered effective if the benefits are clinically significant. As with drugs, there are no perfect intermediate outcomes to be used as surrogates for clinical outcomes in trials of devices, but CDRH must often rely on them. Moreover, many important PMA devices are chronic implants where significant device failures may occur after the intermediate time point assessed in a usual FDA device approval trial. As a result, CDRH relies

heavily on a "total product life cycle" regulatory strategy where post market approval studies are an important and necessary part of device assessment.

All the principles of good clinical trial development and conduct discussed in this text are relevant for planning an appropriate device development strategy. It is therefore often the case that when assessing new types of medical device technologies, a randomized clinical trial will be required for demonstration of safety and effectiveness. However, when considering the often small to moderate iterations that occur over time for a particular device and/or the maturation in basic device design that often occurs for a given device area, it may be reasonable to consider other trial designs (i.e. nonrandomized) as being appropriate for demonstration of safety and effectiveness. The usual cautions apply to the use of nonrandomized designs. Reference to the FDA CDRH guidance document on Clinical Trial Design of Device Trials as well as consultation is therefore recommended [55].

Given that many devices are no longer totally or predominantly external, but may be implanted and remain in the body for some years (e.g., pacemakers, defibrillators, stents), concerns about adverse events occurring long after the device implantation also need to be considered. The optimal system for medical device development and regulatory approval remains controversial. Unlike the U.S., the European System of Regulation does not require demonstration of clinical effectiveness for high risk devices prior to approval. On the other hand Dhruva [56] and Redberg [57] using a drug-centric series of metrics suggested that there were possibly major problems associated with the current U.S. device approval system. Dhruva et al. [56] assessed what kinds of studies were conducted to support approval of 78 high-risk cardiac devices. Of the 123 studies, only 33 were randomized clinical trials. Only about half of the primary outcomes were compared with controls and almost a third of these were retrospective. Almost 90% of the primary outcomes were surrogate measures such as lesion revascularization or lead implant success.

Redberg [57] has suggested that lack of sham controls is often a major weakness of device clinical studies. The placebo effect can be so great that seemingly large benefits may not reflect a true intervention effect. She cites the apparent benefit for treating hypertension from radiofrequency ablation of renal artery nerves. Only when an FDA required trial using sham treatment for the control group was conducted, was lack of benefit (versus the blinded control) observed [58]. A similar situation occurred with laser transmyocardial revascularization, in which open-label trials of using lasers to create myocardial channels resulted in substantial improvement in angina. When a sham-controlled trial was conducted, the sham procedure was equally effective [59]. Much earlier, devices such as intermittent positive pressure breathing (IPPB) for patients with advanced chronic obstructive pulmonary disease were in wide spread use before a clinical trial with a control group demonstrated no clinical benefit [60]. Their use was based on the ability of the device to deliver a treatment deep into the lungs using the pressure gradient.

Objections to requiring conduct of clinical trials with control arms and clinically important outcomes include the fact that many devices have frequent modifications so that a formal clinical trial for each modification would not be feasible.

In addition, many device manufacturers are small companies that do not have the human and financial resources to conduct large trials. Requiring a late phase trial for every device and every modification would not be feasible for them or even for large companies.

Rome et al. [61] looked at FDA approval of cardiac implantable electronic devices originally and as supplements. The authors found that from 1979 to 2012, the FDA approved 77 original devices with an average of 2.6 supplements per device that involved design or other major modifications. For those approved supplements that involved major design changes from 2010 to 2012, less than a quarter (15 of 64) provided clinical data.

Yet randomized clinical trials of devices compared to best standard of care, using objective and clinically meaningful outcomes, are feasible. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial [62] compared a pacemaker alone and a combination of pacemaker and defibrillator against best standard of care in a New York Heart Association class III or IV heart failure population. The primary outcome was all-cause mortality plus all cause hospitalization. Over 1,500 patients were randomized in a 2:2:1 ratio. For the primary outcome, the two intervention arms were statistically and clinically superior to standard of care (approximately 20% relative reductions in events). For the secondary outcome of all cause mortality and cardiovascular hospitalization, approximately 30% reductions were observed in each device arm. The pacemaker-defibrillator arm had a 43% relative reduction and the pacemaker alone arm a 24% reduction in mortality, both being highly significant statistically.

Despite the argument that increasing clinical trial requirements for new or improved devices would discourage and lessen investment in device development and innovation, we think that many medical devices could and should be evaluated according to the fundamentals presented in the previous chapters.

Interventions: Biologics

From a legal and regulatory perspective, biologics products, which replicate natural substances in human bodies such as enzymes, antibodies, or hormones, are generally similar to other drugs. Some, such as vaccines and blood products, are regulated by the Center for Biologics Evaluation and Research (CBER), whereas others, such as anti-TNF agents, are regulated by CDER. Although they are regulated under different acts, the standard requiring that biologic agents be "safe, pure, and potent" is considered to be equivalent to other drugs being "safe and effective" [63]. However, there are some differences (Siegel J, personal communication). First, most biologics are immunogenic. Immunogenicity affects pharmacokinetics, safety, and efficacy. Immunogenic toxicity can be very prominent for some biologics and very serious. Second, biologics have high specificity and are much less likely to have off-target effects than other drugs. Toxicity, therefore, may be more predictable. Off-target effects (e.g., on liver, cardiac

rhythm, bone marrow) are less common, although still may occur. Third, biologics usually do not compete with other drugs for clearance so interactions tend to be less common. Biologics, though, can induce liver enzyme production, and can have interactions related to their pharmacodynamics, rather than their metabolism. Fourth, manufacturing biologics in a consistent manner is more difficult than with other drugs, as is characterizing them. Thus, investigators in phase III trials have a strong incentive to use the same commercial process that would be used after approval in preparing the biologic materials to minimize the challenge of showing that the commercial material is comparable to the clinical trial material.

Finally, it has been argued that producing generic versions is far more difficult. Many think that because it is far more difficult to demonstrate that two biologic products are identical, the term "biosimilar" is preferable to generic [64–66]. This has implications for how much clinical data is required for each, presumably comparable, product. Generic drugs, by definition, have the same active pharmaceutical ingredient as the reference product. As a result, they can be developed by referencing data from an approved product without clinical testing other than bioavailability. Due to limitations in the ability to manufacture and characterize biologics, one cannot ensure that two products are the same, and, even if they were, one cannot know that. Therefore, biologic generics are not technically possible at present. Due to this broadly accepted fact, unlike for small molecules, there is no law or regulatory pathway to have a generic biologic in U.S., in EU, or much of the rest of the world. As one cannot have abbreviated development pathways based upon the same approved product indication (as for generics), abbreviated pathways were created (part of the Affordable Care Act in the U.S.) allowing the referencing of an approved product where a high degree of similarity has been shown, i.e. biosimilars pathways. But similarity as opposed to sameness leaves more potential for clinically meaningful differences, so biosimilars pathways envision that usually some amount of clinical testing will be required to rule out such differences.

Post-trial Requirements

At the end of the clinical trial, regulatory agencies will expect a complete submission of the data in a format that is acceptable to the agency [67, 68]. The ICH document E6 [29] lists the documents that are considered important for the regulatory agencies to have on file, although this list is designed for what is needed for approval of new drugs and may not be applicable to pragmatic trials. These documents include the protocol and any amendments, informed consent materials, sponsor-investigator financial and other arrangements, ethics review committee approval, master randomization list, enrollment logs, source documents, completed case report forms, serious adverse event reports, investigator brochures and any updates, and product accountability.

The following discussion refers primarily to U.S. FDA requirements. However, similar requirements exist in other countries. Sponsors and/or investigators may face three regulatory issues. First, if the trial shows efficacy of an intervention and regulatory approval is sought, documentation in support of the efficacy claim has to be submitted to the FDA, generally through the sponsor or the manufacturer. Second, if the regulatory agency decides to bring the case to a public FDA Advisory Committee meeting for recommendations, the investigators may be called upon to present the trial findings to and answer questions by the committee. Third, FDA approval for marketing of the intervention in the U.S. may require additional post-marketing clinical investigations.

In January of 2015, the Institute of Medicine (IOM) released a report on "Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk" which calls for sharing of patient level de-identified data after study results have been published or after trials have been submitted for regulatory review [69]. While these are currently recommendations by the IOM, they are likely to also be adopted by many sponsors of clinical trials.

Documents for FDA submission

Many regulatory provisions govern the types of documents that need to be submitted in connection with a clinical trial that shows efficacy of an intervention and supports a marketing application. The documents discussed below are not an exhaustive list of those that must be submitted. In addition, from a scientific standpoint, the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the effectiveness claim. The FDA guidance on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products [70] provides some general considerations on the documentation of the quality of evidence supporting an effectiveness claim. It notes that when submitting the requisite quantity of data to support approval of a new product or new use of an approved product, regulations state that sponsors must also document that the studies were adequately designed and well conducted. To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the FDA, and detailed participant records are available at the clinical sites. Providing written standard operating procedures and statistical analysis plans (as well as the charter for a data monitoring committee, if one was used), and the interim reports the committee reviewed along with minutes of those meetings are also part of the documentation. Documentation tends to be very extensive for sponsors and investigators.

Advisory Committee Meeting

Advisory committees, which are convened when the FDA desires external advice around a drug or device approval, provide independent advice to the FDA on a range of issues, including those relating to a specific drug, device or biological product [71]. FDA regulations and guidelines concerning advisory committees do not address what is expected from clinical investigators in the preparation for advisory committee meetings since most of that responsibility rests with the trial sponsor. It is possible that in practice a sponsor-applicant may seek assistance from the trial investigators when preparing these background materials. This assistance could include oral presentations of the trial results or an overall summary of the product's benefits and harms at the advisory committee meeting as well as written summaries of the trial design, conduct, and results. The summary information often includes, among other items, clinical pharmacology and dosing evaluations, clinical efficacy data, and clinical safety data.

Post-approval Issues and Postmarketing Investigations

Postmarketing clinical investigations are subject to many statutory and regulatory requirements if they have the potential or intent to support a product label change. They are often conducted under an IND and therefore may be subject to the IND requirements. Postmarketing reporting of adverse events and submissions of an annual report are also generally expected. When the product has been approved on the basis of a clinical trial, postmarketing clinical investigations may be *required* if there is new safety information or there is need to verify clinical benefit. Postmarketing clinical investigations can be *requested*, as agreed-upon in postmarketing commitments, if needed to further evaluate efficacy and safety in a product that has undergone traditional approval.

Certain postmarketing clinical investigations must be registered and have results submitted to ClinicalTrials.gov in a timely fashion. There may be financial penalties or fines for not complying with these requirements. For drugs and biological products, the trial registration and results submission would be required for any "applicable drug clinical trial," which, in general, means a controlled clinical investigation, other than a phase I clinical investigation. Despite the requirement to submit data to ClinicalTrials.gov, many trials either had delays in publication or no publication [72]. One study [73] showed that industry-sponsored trials had a much higher compliance in entering results into ClinicalTrials.gov than non-industry trials, although in neither case did the majority submit results within the mandated 1 year. Low rates of data submission were also found by Jones et al. [74]. Another study suggested that the high data submission rates to ClinicalTrials.gov were limited to late-phase trials [75].

The generally low rates of data submission are perhaps due to inadequate understanding of the requirements by the investigators. It is important that all investigators know that trials conducted under FDA regulations or with funding from the National Institutes of Health need to have the data submitted to ClinicalTrials.gov. A proposal in 2014 to expand the number of trials funded by the NIH that are required to have their data entered into ClinicalTrials.gov [76] should be noted.

For many years, regulatory agencies have solicited reports of adverse events that have occurred in clinical practice, after a drug or device has been approved and is marketed. As discussed in Chap. 12, even large trials of long duration may miss important adverse effects. Only after something has been used in many different people for sometimes years will some adverse effect be identified. Follow-up is even more important for products that are approved and marketed without trials that monitor important clinical outcomes. For example, for drugs approved on the basis of surrogate outcomes, and when the trials were therefore either too small or too short to obtain sufficient numbers of clinical events, post-marketing reports become extremely important. However, given the lack of a rigorous control group, postmarketing reports can be misleading [77]. Pressures and incentives to approve products more quickly, particularly for life-threatening conditions for which there are few if any treatment options, has led to regulatory changes for so-called "breakthrough drugs" [19, 78, 79]. While the law does not allow a different standard for use of intermediate markers as surrogates with rare diseases than for other more common diseases, still requiring a confirmatory clinical outcome trial, the use of surrogates or biomarkers may be necessary with rare diseases for which a sufficiently large trial with a clinical outcome is difficult or even impossible [80, 81].

For products that have had accelerated approval, whether drugs, devices, or biologics, the pre-approval clinical information is far more limited than for products that have undergone clinical outcome trials. Part of the accelerated approval process calls for additional post-approval clinical assessment, including adverse event monitoring [19]. Sometimes, actual clinical trials are required after accelerated approval. As discussed in the section on drug interventions, the FDA approved bedaquiline for a serious unmet need using the first of a new class of drugs to treat drug-resistant tuberculosis [47]. This was done on the basis of a phase IIb placebo-controlled trial on an expedited approval path, with the requirement that a confirmatory trial would be conducted, though not completed until 2022 [79]. Approval decisions are often difficult and controversial. There are added complications when expedited approval is used, involving the weighing of many factors. As in the case with bedaquiline, advisory committees and regulatory agencies need to use considerable judgment, balancing early access to the benefits of important therapeutic early interventions against possible longer term harms.

More rapid approval of drugs may lead to identification of more adverse effects after marketing. Frank et al. [82] noted an association between a greater number of "boxed" warnings in drug labeling and actual drug withdrawal for safety concerns and acceleration of FDA drug approval. However, association does not demonstrate

causation and even if an association reflects causation, the balance between any benefits from faster approval and the harms discovered later is unknown.

An FDA web page on postmarketing requirements and commitments may provide useful information [83].

Key Links

It is essential that all investigators conducting trials that are, or might be, subject to regulatory approval, keep aware of current regulations and guidances. Key links are shown here:

International Conference on Harmonisation

ICH Official Web Site: http://www.ich.org/
Efficacy Guidelines: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
Safety Guidelines: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html
MedDRA: http://www.ich.org/products/meddra.html

U.S. Food and Drug Administration

FDA Home Page: http://www.fda.gov/
FDA Guidances: http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/Guidances/default.htm
Conducting Clinical Trials in Drugs: http://www.fda.gov/drugs/developmentapprovalprocess/conductingclinicaltrials/default.htm
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm#form1571
Conducting Clinical Trials in Devices: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf
Conducting Clinical Trials in Gene Therapy:

Early phase clinical trials.
http://www.fda.gov/downloads/Biologi. . ./UCM359073.pdf
Observing subjects for delayed adverse events. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm

European Medicines Agency

EMA Home Page: http://maintenance.ema.europa.eu/
Clinical Trials in Human Medicines: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp&mid=WC0b01ac 058060676f

Health Canada

Health Canada Home Page: http://www.hc-sc.gc.ca/index-eng.php
Guidance Document for Clinical Trials Sponsors: clinical trial applications: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec- eng.php

Pharmaceuticals and Medical Devices Agency, Japan

Home Page: http://www.pmda.go.jp/english/
Ministerial Ordinance on Good Clinical Practice for Drugs. http://www.pmda.go.jp/english/service/pdf/ministerial/20130329No_28.pdf

Bioethics Resources

http://bioethics.od.nih.gov/IRB.html

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7. Code of Federal Regulations (21 CFR 50). http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50
8. Office for Human Research Protections (OHRP). http://www.hhs.gov/ohrp/
9. Food and Drug Administration: Clinical trial guidance documents. http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm.
10. ClinicalTrials.gov. https://clinicaltrials.gov/
11. FDA: Certifications to accompany drug, biological product, and device applications/submissions. http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm
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