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Institutional Review Boards and Independent Ethics Committees

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Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs) are charged with protecting the rights and safety of clinical trial participants. The regulations that guide the review, approval, and conduct of human research refer to these independent boards as IRBs or IECs. In 2001 the Association for the Accreditation of Human Research Protection Programs (AAHRPP) was formed. Since that time many institutions have reorganized the various support and review services connected with human subject research including the IRB as one component of their Human Research Protection Program (HRPP). Similarly to the IRB, these programs have as their primary mission the protection of human research subjects. Some IRB responsibilities such as clinical trial monitoring, investigator and research participant education, and auditing of research records may be shifted to specialized units within the HRPP. These programs may also facilitate investigator–sponsor relationships to promote safe, ethical research practices. In many institutions in the USA the committee also serves as the Health Insurance Portability and Accountability Act of 1996 (HIPAA) privacy board for research-related activities.

There are at least three systems used by institutions to fulfill human research ethics review requirements.¹ It is important to determine the IRB that will be responsible for reviewing and approving the research. Some institutions require their own IRB to review all research, while others rely solely on the use of a central IRB, or permit central IRB review for certain types of studies. Central IRBs are particularly useful for multicenter studies because only one IRB is responsible for approval of the protocol and informed consent form. This can make meeting this regulatory requirement more efficient. The possible advantages and disadvantages of central versus local IRB

review have been well described by Fitzgerald and Phillips.¹ A potential concern when using a central IRB surrounds the ability of that committee to understand relevant local issues. Local issues typically relate to the capabilities of the Principal Investigator (PI) to carry out the research, the adequacy of institutional resources to safely perform the research, and any considerations that should be given to potential study participants such as cultural or economic factors. In the European Community where a national health agency can attest to the capabilities of the clinician and institutional resources, some argue that there are no local issues related to whether the research is ethical or not.² The premise is, in theory, true; yet it is founded on the assumption that all good clinicians will be good researchers. Considering the current regulatory mandates, it is unlikely that the requirement for review and approval of research by local IRBs will be abandoned in the near future. Given this, sponsors and investigators should make certain which IRB review process applies to their study.

Composition, procedures, and function

Composition

The IRB must consist of at least five members reflecting diversity of scientific and non-scientific backgrounds and professional specialties and also cultural interests, include both sexes, and have at least one member who is not affiliated with the institution directly or through a family member (usually referred to as the community member). While the minimum number of members is set at five, most IRBs will consist of slightly more to accommodate additional expertise and to assure that a quorum can be convened to conduct the meeting. A factor that drives committee composition is the nature of research that is reviewed. Through regulations, the International Conference on Harmonisation (ICH), the Department of Health and Human Services (DHHS), and the Food and Drug Administration (FDA) require that IRBs consist of members who collectively have sufficient expertise to evaluate the quality of the science, medical aspects of the proposed research, and the ethics of conducting a study. The net effect of this regulation is to require that at least one member of the committee be a physician, since there is no other way to obtain the expertise required to evaluate the study's medical aspects. IRBs are permitted to use an alternate member system, where the alternate member may attend if the primary member is not available. Also, the IRB may invite outside consultants if necessary to provide insight into scientific or ethical issues that are beyond the expertise of the convened committee. While consultants can assist in the review of a protocol, they cannot participate in the voting for approval of the research.

IRB membership is also influenced by the population eligible to participate in the protocol. Vulnerable populations specifically addressed in the DHHS, FDA, or ICH regulations include children, prisoners, pregnant women, fetuses, and the handicapped and mentally impaired. In order to review research that includes these participant groups, the regulations require that individuals with expertise about those populations and who understand how they might be vulnerable be included on the committee. However, these are by no means the only potentially vulnerable groups of study participants. Students can be vulnerable if participating in research being conducted by a faculty member. Similarly, employees and staff members might be considered vulnerable if asked to participate in research directed by the department head. The IRB needs to be cognizant that there are a number of social, economic, and cultural reasons that might make an individual vulnerable. Furthermore, the underlying disease state and clinical prognosis can affect how the patient perceives the planned intervention and may create vulnerability.

Unlike the ICH and DHHS, the FDA requires committee membership that can assess the proposed research according to ‘acceptability . . . in terms of institutional commitments.’ The effect of this section of the regulations is to allow an institution to restrict research that falls outside of its standards or places an undue burden on institutional resources. While an institution might prohibit IRB-approved research from being conducted, the institution cannot permit the conduct of research that has not received IRB approval.

Procedures and functions

The requirements for IRB operations and procedures are described in 21 CFR Part 56, Subpart C, and ICH E6 Sections 3.2 and 3.3. These sections identify what must be accomplished to be in compliance with the regulations, and does not recommend specific methods that must be implemented. Thus, each institution establishes its own policies and procedures to achieve the goal of protecting the rights and safety of human research participants. Because of this, it is in the best interest of the sponsor to work with investigators experienced with the IRB submission requirements of the institution. FDA and ICH regulations both require that IRBs follow written procedures for initial and continuing reviews, the frequency of continuing reviews, prompt reporting of changes to the research, prompt reporting of unexpected events, adverse reactions, and deviations from or non-compliance with the protocol. Under FDA and ICH regulations, IRBs can approve a research protocol, require modifications to the protocol in order to gain approval, disapprove the research, or suspend or terminate research that has already received approval. The IRB’s determination must be communicated in writing within a ‘reasonable time’ and should provide specific recommendations for changes needed to secure approval, or if approved, the conditions of approval.

The ICH E6 *Guideline for Good Clinical Practice* is written primarily for research that requires full board review at a convened meeting. Expedited review (i.e., review conducted by the IRB chairperson or designee) is mentioned only as it relates to ‘minor changes’ to a protocol that has already received full board approval. In contrast, FDA regulations identify categories of research that can be exempted or follow an expedited review process and do not go to full committee. Of the four categories of research that qualify for a review exemption, the one most pertinent to IRBs that review biomedical research concerns the emergency use of an investigational drug or device. The first use of an investigational drug or device in an emergency situation is exempt from IRB review; however, such use must be reported to the IRB within 5 working days. Any subsequent use of the drug or device at that institution requires the approval of the protocol at a convened meeting of the full IRB. Research that qualifies for expedited review and approval is no more than minimal risk or for minor modifications of research that has already receive full board approval. Examples of research that is exempt from review or may be expedited under DHSS regulations are found

Table 8.1 Categories of exempt research

- 1 Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- 2 Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
- 3 Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- 4 Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- 5 Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.
- 6 Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the US Department of Agriculture.

Table 8.2 Categories of research that may be reviewed by expedited procedures

Research activities that present no more than minimal risk and fall into one of the following categories are eligible for review expedited by the IRB through the expedited review procedure.

- 1 Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
 - a Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - b Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- 2 Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - a from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 mL in an 8 week period and collection may not occur more frequently than 2 times per week;
 - b or from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 mL or 3 mL per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
- 3 Prospective collection of biological specimens for research purposes by non-invasive means.
- 4 Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving X-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)
- 5 Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).
- 6 Collection of data from voice, video, digital, or image recordings made for research purposes.
- 7 Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
- 8 Continuing review of research previously approved by the convened IRB as follows:
 - a where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
 - b where no subjects have been enrolled and no additional risks have been identified; or
 - c where the remaining research activities are limited to data analysis.

Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

in Table 8.1 and Table 8.2. Most research that involves a drug or device will exceed the criteria for minimal risk and will require full board review.

Protection of human subjects

The process for the protection of human research subjects is multifaceted. The underlying principles for the protection of research subjects are found in the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report,

which were discussed in Chapter 1. The charge to IRBs is to apply these principles in the evaluation of every aspect of the proposed research activity to protect the rights, safety, and well-being of study participants. Concurrent with this, the IRB staff assists investigators in maintaining adherence to regulatory mandates and institutional policies. It is not surprising, therefore, that when a research protocol is submitted to multiple IRBs the final determinations of the committees, their questions, and requests for additional information can vary greatly.^{3,4}

Stress has been placed on the IRB by ‘mission creep’: the real or perceived need to consider all potential risks, not just to study participants but potential risks to researchers and the institution itself.⁵ As part of the research approval process, IRBs will also consider issues that might not appear directly related to research risks such as investigator and/or institutional conflicts of interest, the scientific validity of a study, as well as the secure storage of and appropriate access to research records. Increasingly many sponsored trials request (or require) the collection and storage of biological specimens for future research, which presents another series of challenges for IRBs. This may be particularly problematic when studies using DNA are reviewed because of the potential to stigmatize certain ethnic or cultural groups.⁶ It has been suggested that IRBs consider the risks to third parties (individuals not directly involved in the research) depending on the degree of risk to them.^{7,8}

For many situations encountered by the IRB, there is little in the way of regulatory guidance. As a result, IRBs may establish substantially different submission requirements and review processes to fulfill regulatory mandates. The ultimate impact of these added responsibilities and diversity of review approaches is the potential for delays in starting the research. The effort required to ensure the adherence with regulatory and institutional policies also diverts IRB efforts from its primary mission of protecting the rights and welfare of human research participants.⁵

The materials that the IRB should obtain and review to make an approval determination are listed in Table 8.3. It should be noted that FDA regulations do not explicitly require that the committee obtain the Investigator’s Brochure (IB). The need to review the IB is inferred from CFR 21.56.111, where the IRB is required to assess risks and determine that the risks are reasonable in relation to the anticipated benefits. Sponsors and investigators do a remarkable job in making these materials available to investigative teams and the IRB. The process may be particularly onerous in some institutions where ‘hard copies’ (as opposed to electronic copies) must be submitted. Despite providing all of this information, sponsors and investigators still encounter difficulties in obtaining IRB approval. This suggests that the major problem is not a lack of information, but failure to provide the information in the format and detail the IRB needs to conduct its review. Alternatively, sponsors and investigators may not understand the IRB review process or the IRB may not

Table 8.3 Documents the IRB/IEC should obtain

Materials submitted	IRB considerations	Potential problems
Trial protocol(s) and amendment(s)	The protocol is current and all amendments have been incorporated or appended.	All protocol elements are not adequately detailed. This frequently occurs when biosamples are being collected. See Table 6.3.
Investigator's brochure	Currently approved IB	IB lacks required information. Studies referred to in the protocol not detailed in the brochure. Is the brochure submitted the most current?
Written informed consent form(s) and consent form updates	Reading level. Adherence to local IRB requirements for the format and any standard language.	Failure to follow local IRB consent form template. Use of consent form language that differs substantially from institutional standards. Incorporating HIPAA language into the consent when the institution uses a standalone HIPAA authorization.
Subject recruitment materials	Provides sufficient detail to inform the potential participant of study requirements, duration, and compensation.	The recruitment process does not protect the patient's confidentiality, and/or privacy. Will patients receive unsolicited phone calls or letters?
Written information to be provided to subjects	Reading level. Not coercive. Indicate that the materials are related to a research activity.	Reading level is appropriate, but problems exist with type size and ease of use.
Available safety information	All of the available information regarding preclinical studies and sufficient safety data to support the use of the test article for the expected duration of participant enrollment.	Although usually provided in the IB, additional preclinical and clinical data, or safety reports may exist that have not been incorporated into the IB.
Information about payments and compensation to subjects	Compensation should not create an unfair inducement for study participation. Timing and method of payment should be clear. Pro-rating for partial study completion should be explained.	The process should be clear to the IRB and the study participant. Some institutions require that a W-9 be completed before processing a check. This should be reflected in protocol and consent form.
Investigator's current curriculum vitae and/or other evidence of qualifications	Licensure and training necessary to safely perform all study-related activities. Inclusion of other study team members where special expertise is required.	There are many laboratory tests and clinical procedures that are used for screening and monitoring. It should be clear that qualified individuals are being used to interpret this information.
Any other documents required by the IRB/IEC	Completion of an IRB-approved course in human subjects' research.	Not all investigative team members have completed IRB training. This will delay study start.

have done a sufficient job of communicating its needs to those seeking to conduct the study. Further complicating matters is the lack of research and guidance on how IRBs should approach the review and approval of research.⁹ The sections that follow are not intended to provide the details of the various documents reviewed by the IRB. Instead, they highlight the kind of information generally expected to be available to IRB members when protocols are discussed.

Review of the protocol, Investigator's Brochure, and informed consent

The IRB bases its decisions largely on the review of the documents provided by the sponsor and the PI. While the sponsor provides the bulk of materials that need to be submitted to the IRB, it is up to the investigator to ensure that the application is made in accordance with local IRB policies and procedures. Failure to 'follow the submission guidelines' occurs frequently and may result in delays in starting the study.¹⁰ Some IRBs may invite the PI to the IRB meeting to present the research protocol and to clarify study-related issues, but even with this additional input, written documentation will be needed to support the basis of IRB's decision.

For industry-sponsored trials the protocol and IB are developed by experts in their field of research. As a result the need for the study, the design, and procedures required by the protocol most often have a sound scientific basis. Roadblocks may be encountered when these documents are submitted to the IRB for 'local review.' Regulatory authorities require local review to ensure that research subjects' rights are protected, taking into account the unique characteristics of the population served by the institution (e.g., religious, cultural, or economic) as well as the ability of the investigators and the institution to provide the care and services required by the protocol in light of existing commitments and resources. The problems encountered as a result of the local review of research are well documented.^{2,11-13} Yet, for the foreseeable future it is not likely that the requirement for local review will change. Given this, there are steps that can be taken by study sponsors and investigators to minimize these difficulties as discussed below.

Protocol review

The research protocol is the principal document the IRB uses to determine whether the research should be approved at all. Depending on institutional requirements, one or more copies of the sponsor's full protocol will need to be submitted. The protocol should be the most current version and should have already incorporated any preexisting amendments. Many IRBs use a primary reviewer system whereby one member receives a copy of all original study

documents. When this process is used, the IRB usually requires the submission of a protocol summary, which highlights the key aspects of the trial and is distributed to all committee members. The protocol summary is not as detailed as the full protocol but provides sufficient information for the committee to understand the key components of the research. These components include a brief overview of the condition being treated, inadequacies of current therapeutic interventions, the rationale of the study, the purpose of the study, identification of the primary outcome parameter, eligibility requirements, the treatment plan, the risks and how these have been minimized, the benefits, alternative treatments, sample size estimation, the primary and secondary outcome parameters, and plans for statistical analysis.¹⁴ Because IRBs consist of members with scientific and non-scientific backgrounds, as well as community representatives, protocol summaries need to be written in uncomplicated language and avoid technical jargon. Sponsors and investigators should not assume that what is clear to them will automatically be clear to all IRB members.

Background

A short section providing the background of the condition being treated should be included. Most committees will not need extensive education about commonly encountered disease states such as hypertension, heart failure, or diabetes. But even in these conditions the proposed intervention might be directed at one component of the disease such as peripheral neuropathy, management of edema, or preserving renal function. In these circumstances, the background material should provide a basis for the committee to conclude that the intervention has the potential to improve or favorably alter the course of the disease. The FDA or the European Medicines Agency (EMA) may have published a guidance document that impacts on the design of the study. The guidance might suggest the need for a placebo arm, or recommend specific efficacy or safety criteria. IRB members, and sometimes the local investigators, are not always aware that the protocol was designed to conform to a specific guidance. A simple statement in the background that informs the committee of the guidance will facilitate their review.

Lack of details within the protocol can generate questions from the IRB and slow the process. While the purpose of the study might be clear (compare new drug A with established drug B), the rationale for conducting the study may not be readily apparent. Is the rationale that not all patients respond to the established drug so a new drug is needed? Or does the new drug have a better side-effects profile or offer the prospect of a more convenient dosage form or less frequent dosing? This information helps IRB members to understand why the study is important and should be conducted. It also introduces the prospects for potential benefit for study subjects and others with the underlying condition. The committee will want to see the rationale presented to study subjects in the consent document.

Primary outcome parameter

Identification of the primary outcome is essential to the conduct of the research, and should be clearly defined. The protocol should provide the basis for selecting the primary outcome variable and how it will be accurately measured. Some studies may use a primary outcome parameter that is a surrogate for the benefit the intervention is expected to achieve. For example, a study of an antihypertensive agent might use blood pressure lowering as an outcome although the real goal is to reduce cardiovascular morbidity and mortality. The sponsor should provide the rationale as to how the outcome is associated with the disease process being investigated. For comparative studies, the protocol should not only address the differences in outcome measures that can be shown to be statistically significantly different, but should also explain whether those differences have any clinical significance.

Eligibility criteria

IRBs look carefully at the eligibility criteria for the study. Inclusion and exclusion criteria are the first step the sponsor and investigator make in protecting study subjects. Again, adequate details should be provided to define the study population. The eligibility criteria should not be expressed in generalities (normal renal function) when specific criteria can easily be defined. Some protocols might define normal renal function as a serum creatinine <1.5 mg/dL; others as a creatinine clearance >80 mL/min. If the later definition is applied, how is this determined? Was it a 24-hour urine collection or an estimated creatinine clearance? If estimated, which formula is being used? The protocol should clearly state when eligibility assessments will be performed in relation to obtaining informed consent from the subject. The committee will look to determine whether eligibility is based on clinical and demographic information that already exists as part of the usual care the individual receives or whether eligibility will be determined on the basis of information collected and procedures performed solely for the purpose of the research. These and other issues will impact on inconveniences to the subject and may result in having to withdraw a subject who is no longer eligible to participate.

Study intervention and procedures

While the background, purpose, and eligibility criteria of the research generally raise few questions from the IRB, the procedures and interventions identified in the study methodology represent potential sources of risk, and thus receive very careful IRB attention. The IRB should consider all possible sources of risk. Some of these, such as the use of an investigational device or drug and research-related procedures, are easily recognized. Others such as inconveniences due to travel, emotional harm, and loss of confidentiality may be difficult to ascertain or may result from local conditions and therefore not

be fully addressed in the sponsor's protocol. It is particularly helpful to the committee if the protocol identifies the interventions that are standard of care and those that are done solely for the purpose of the study. Input from the PI at each site is essential in making this determination since what represents standard of care at one institution may not at another. IRB members look for specific information in the protocol as it relates to the source of risk. In biomedical research, IRBs frequently consider the risks of drugs, devices, and study-related procedures. When the drugs and devices are investigational, the sponsor must assume the primary role for informing the committee. Individual investigators generally are not familiar enough with the drug or device to answer specific questions even if they have attended an investigators' meeting. Some of the information that IRBs will want to review may exist in the IB, but as mentioned above, not all members may receive a copy of the IB prior to the meeting. Furthermore, some elements of the methodology result from decisions made internally by the sponsor during protocol development or may be required by regulatory guidances and it may not be easily discernible why they were included.

Drug-related risks

In the case of a drug not yet approved for marketing, the extent of information available can vary considerably. Findings may be limited to the results of animal testing (for first-in-human studies) or may be much more substantial, reflecting the drug's tolerability and efficacy based on the exposure of thousands of study participants. To facilitate protocol review, the sponsor should incorporate the main findings of the pre-clinical and clinical studies reported in the IB into the protocol. The committee will be looking for justification of the dose and duration of treatment. For example, how did the pre-clinical studies influence the selection of the dosage that will be tested in humans? How does tolerability shown in a two-week human safety study support the transition to a six-month efficacy study? Most IRBs will not have the expertise to make an extrapolation of the results of animal testing to first-in-human studies and conclude that the dose being tested is safe. In order to facilitate the review process, it is worthwhile for the sponsor to address these issues in the protocol to educate the IRB about the regulatory guidances and scientific basis for the dose and duration of drug exposure. Issues surrounding dose selection for early clinical trials will become more complex if sponsors more actively pursue microdose studies or other FDA drug development initiatives.¹⁵

While not an infallible method for predicting Adverse Events (AEs), identifying similarities in structure or pharmacological activity of the investigational drug to those of marketed products with established side-effect profiles provides valuable information to the committee. The question raised by Cohen, 'Should we tolerate tolerability as an objective in early drug

development?’ relates directly to the drug safety concerns of the IRB.¹⁶ Early-phase trials provide the opportunity to characterize a drug’s kinetics and dynamics, which can then be used to inform the next series of human trials. Most committees review early-phase clinical trials with the understanding that rare, but serious, AEs are not likely to be identified even after substantial numbers of subjects have been studied.¹⁷ While it is unlikely that an absolutely safe drug will ever be marketed, IRB members are very aware that a number of medications have been approved and marketed only to be withdrawn shortly thereafter because of rare, but serious side-effects. If the medication is not withdrawn from the market, regulatory authorities might require the addition of warning statements or restrict the types of patients who should receive the drug. Lacking any information to the contrary, these warnings might be extended to the whole class of drugs. This can impact on the IRB’s assessment of risks for investigational drugs that are pharmacologically or structurally similar to the drug that was withdrawn. For this type of drug, the sponsor should not only include but highlight the portions of the protocol that identify and minimize the potential for this AE.

Device-related risks

Regulatory approval prior to the initiation of a device trial is required in the USA and Japan as opposed to the European Union, which has been suggested to impact development costs and the rapidity of bringing new devices to market.¹⁸ Most countries have established criteria for classifying medical devices based primarily on the potential for risk. Some of the factors that are considered in making this determination include the characteristics of the device (invasive vs. non-invasive), duration of use (short-term vs. long-term), and the need for specialized training for safe and effective use of the device. The FDA identifies devices as ‘significant risk or non-significant risk.’ However, this determination applies only to the device and not to the manner in which the device will be used in the study. It is possible, therefore, that a non-significant-risk device could be determined by the IRB to be a significant-risk device on the basis of its intended use, the patient population being studied, or the consequences of device failure. In the USA, IRBs are also responsible for the approval of humanitarian use devices (HDEs) within their institutions. These are devices intended for use in conditions likely to affect fewer than 4000 patients yearly, making the conduct of a clinical trial nearly impossible. Many IRBs will have little or no experience with this type of device, so the sponsor should be prepared to educate the committee members by providing regulatory guidance information and identifying the sponsor’s responsibilities.

Procedure-related risks

Study-related procedures contribute to the overall risks associated with the protocol, even if they are not experimental in and of themselves. It is of great

value to the committee if the sponsor and PI clearly delineate those procedures that are considered standard of care from those performed solely for the purposes of the study. Making this determination is not always easy and can vary among research sites depending on local practices and the expertise available.¹⁹ For example, the standard of care for certain conditions might be to obtain a chest radiograph at yearly intervals. The protocol might require that the study participant have had a chest radiograph performed within the previous six months. If a patient's last radiograph was obtained nine months ago, a radiograph will be required to qualify for the study. This is not part of the standard of care, so the radiation burden, though minimal, is still attributable to the research. Depending on the institution, the PI may be required to submit the protocol to a committee separate from the IRB for an assessment of radiation risks. The number and frequency of study visits might also be in excess of what would be considered standard of care; thus contributing to the inconveniences experienced within the study. It is imperative that the sponsor work closely with the site's PI to identify local issues related to study procedures.

Another kind of procedural risk relates to the need to withdraw other therapies in order to qualify a patient for the study. Today, most diseases have at least one drug, and sometimes dozens of drugs, indicated for the treatment of that condition. It is not unusual, therefore, to have potential participants discontinue medications in order to meet eligibility criteria. While it might be possible to restrict eligibility to newly diagnosed patients, this approach severely hampers study enrollment. Most IRBs are experienced with studies that require withdrawal of what might be very effective therapy for a patient in order to participate in a clinical trial. When effective therapy is withdrawn, the underlying condition would be expected to deteriorate, which might lead to the return of minor annoying symptoms or a disease flare of substantial clinical significance. For those studies in which withdrawal of other therapies is required, the protocol should explain in detail how participants will be monitored to detect worsening of the underlying condition and minimize the duration of poor disease control. In addition, some method of rescue therapy or rescue medication may be included in the protocol as an additional safety measure for patients.

The use of a placebo control group will receive careful attention from the IRB. A complete discussion of the ethical use of placebos in clinical research goes far beyond the purpose of this chapter; however, it is important to recognize that including a placebo control arm in a clinical trial can result in a clash of scientific, ethical, and regulatory principles.²⁰ As mentioned above, multiple therapeutic options exist for most medical conditions. Given this, why should a placebo control group ever be used? Amdur and Biddle have proposed an algorithm for the ethical use of placebos.²¹ They suggest a number of factors that IRBs should consider in evaluating the ethical use of a placebo control in clinical research. Among these are the effectiveness and tolerability of current

treatments, the long-term and short-term harms that might result from placebo use, and the potential value for the treatment of future patients with that condition. Consideration of the ethical use of placebos is not restricted to clinical drug trials. A similar concern exists for studies that might require a sham surgical procedure²² or the insertion of a device that is not activated.²³ Once again, communication between the sponsor and the site investigator is critical, as is providing the rationale for using a placebo in the trial.

Methodology

Separate from study-related procedures is the study methodology. In addition to the general design of the trial (superiority, equivalence, non-inferiority), other aspects of the trial that are important to the IRB include the manner of randomization, stratification based on one or more patient characteristics, blinding procedures, choice of comparator, use of placebo, sample size estimation, and planned data analysis. It might appear that many aspects of the study methods fall outside of the purview of the IRB because they do not relate directly to individual participants' risks. However, they frequently do relate to the collective risks of study participants. For example, the lower boundary for non-inferiority trials must be established in order to estimate sample size.²⁴ The rationale for selecting this boundary should be explained. It might be acceptable to the committee if the inferiority boundary is set at 30% less effective if the comparator is associated with significant toxicities and the consequences of treatment failure are not life-threatening. On the other hand, this margin would likely not be acceptable if the comparator was highly effective and caused minimal toxicity. In either case, the sponsor should provide the rationale for why this lower limit was selected. Individual clinical investigators generally cannot provide a satisfactory answer to the committee, resulting in delays in starting the study.

Sample size estimations are important to the committee. Most often sample size calculations are based on an efficacy end point because it can be clearly defined and the variability in participant response to the intervention can be estimated from responses observed in similar studies of the same disease state. Though possible, it is impractical to base the sample size estimation on safety outcomes due to their unpredictability and low rates of occurrence, which would necessitate a large study population. Despite the relative ease with which a sample size can be determined for most studies, many investigator-initiated trials, and even those supported by NIH funding, may be underpowered to detect a significant treatment effect.^{25,26} Studies conducted by the pharmaceutical industry rarely suffer from this problem but may appear to enroll an excessive number of participants. Studies like this might be 'overpowered' for the primary end point; that is, the clinical question could be answered with fewer participants enrolled. Overpowered studies can create problems during the review process because each of the study

participants will still need to complete all of the study-related procedures (which might include blood sampling and radiation exposure) or be randomized to a less-effective treatment even though the study outcome could be determined based on a smaller number of subjects. Nonetheless, a case can be made for enrolling more than the number of participants required to ensure efficacy in order to better detect rare AEs and improve safety.

The regulatory landscape is changing with regard to the design of clinical trials, driven by the high costs of conducting human research and difficulties in recruiting and retaining study participants. Alternative strategies such as microdosing are being advocated by regulatory agencies.¹⁵ In addition, adaptive trial designs are being suggested that will permit changes in the method of randomization, the doses being evaluated, and even modification of the primary outcome parameter.^{27–30} Many IRBs do not have access to statisticians or others who are well versed in these types of clinical trial methodologies. It is in the best interest of the sponsor to assist committee members by providing the basics behind the design of these trials.

Special concerns related to biobanks

Any experienced clinician is aware that patients differ in their response to a drug. A clinically effective dose in one patient may result in serious toxicity in another. With the development of sensitive analytical techniques, demographic and clinical characteristics such as age, weight, and renal and hepatic function were identified that influence the pharmacokinetic profile of a variety of drugs. Although the kinetics of a drug are still of major importance in understanding the factors that contribute to the efficacy and safety of a drug, differences remain among individuals that cannot be explained by kinetics alone. Increasingly, industry-sponsored protocols are asking study participants to provide a blood or tissue sample to identify genetic polymorphisms that result in a different response among drug recipients. Other uses of banked materials include proteomic and biomarker studies that might be useful in the identification of new therapeutic targets. Despite the extensive detail provided in the sponsor's protocol regarding eligibility criteria, randomization procedures, safety monitoring, and possible adverse effects, the procedures for collection and use of biological samples sometimes receive less than a paragraph within the protocol. This lack of information may result in delays in the approval of this portion of the research. Because the procedures and risks of genetic research are different from other research-related risks, some IRBs require a separate consent form for genetic research. Questions frequently posed by the IRB related to research on stored blood or tissues that should be addressed in the protocol are listed in Table 8.4. Sponsors are responsible for providing this information to the committee as the local investigator will generally not be well versed in how the biobank will be operated and the steps taken to protect the confidentiality of the donor.

Table 8.4 Protocol elements and tissue banks**1.1 Title**

- Should state that it is a tissue bank

1.2 Objectives

- Purpose of the bank, why is it important?
- Who is it for?
- What kind of testing will be performed?

1.3 Background**1.4 Eligibility criteria**

- How are participants identified?
- Will normals be used?
- Samples from outside sources?

1.5 Treatment plan

- How will samples be collected? Departures from standard of care?
- Consider how clinical and demographic information will be handled.
- What types of testing will be performed?
 - Only for the disease the patient has or unrelated? Alzheimer's?
 - Genetic testing?
 - Other disease states? Hep. B, Hep. C, HIV?
- What happens to future test results?
- Procedures for releasing samples to other investigators.
- Plans to compensate for new product development.

1.6 Risks

- Major concern – confidentiality.
- Inaccurate pathological diagnosis.
- Due to alterations in procedures to accommodate specimen collection.

1.7 Benefits

- Generally none for the participant.
- It is fair to include potential to benefit patients with similar conditions; societal benefits.

1.8 Alternative treatments

- Don't participate.

1.9 Data collection and statistics

- Generally not an issue.

1.10 Other issues that should be addressed

- Coded samples – possibility to identify participant.
- Certificate of confidentiality.

Investigator's Brochure

The ICH E6 *Guideline for Good Clinical Practice* describes the recommended content of the IB. Although the protocol describes what will be done during the study and how it will be done, it is the IB that provides the insight as to why certain procedures and monitoring parameters have been incorporated into the protocol. The IB serves as a resource for the IRB and the investigator to determine everything that is known (and what is not known) about the drug or device being studied. For drugs and devices in early development, there may be little or no published literature regarding the product's efficacy or safety. Consequently, in making its judgment for approving a protocol the IRB will rely heavily on the information provided in this document. As with the protocol, questions will be raised based on information that is referred to but not provided or that is not clear. For example, it is not unusual for participant accrual to proceed at a slower than expected rate, which may open the study to sites well after the original start date. Or the IB version submitted by the investigator may be dated two years prior to the date the protocol is scheduled for IRB review. How can the committee know that this is the current version? The IB might also state that extended dosing studies in humans have been started and that long-term toxicity studies in rats are pending. Has this work been completed? Even IBs that are up to date may not include important information. For the IB to state that the chemical structure of the drug is well characterized, while no structure is provided, is a disservice to the committee. Most IRB committees will not have the expertise of a medicinal chemist available to them, but the ability of a clinician to compare the structure with that of a marketed agent with a known side-effect profile can provide a context for expected efficacy and toxicity. Sponsors can help themselves by keeping the IB current and by providing local investigators with information to be shared with the IRB related to studies that are in progress but not yet appearing in the IB.

Informed consent

While considerable attention is given to the consent document, the IRB is equally concerned about the process and timing for obtaining consent. Informed consent is discussed in Chapter 3. The material conveyed here relates primarily to potential barriers that may be encountered by sponsors and investigators to getting the consent form approved.

Some problems are easily predicted and thus avoidable. One of the frequently encountered problems is the inclusion of HIPAA language within the consent document. Some institutions require that HIPAA authorizations be obtained on a separate, study-specific document. The research consent informs participants of the study rationale, procedures, risks, and alternatives,

and their rights and responsibilities. The HIPAA authorization informs participants that as a consequence of their involvement in the study, private health information will be shared with the sponsor, the IRB, and regulatory authorities. Another theoretical reason for separating the HIPAA authorization from the research consent is to minimize institutional liability if either of these documents is found to be deficient in some manner. The local investigator should be able to provide some guidance to the sponsor as to which approach the institution uses.

Another common problem with consent forms lies within the injury statement. This is no doubt the result of the increase in litigation surrounding clinical research, which exposes sponsors, researchers, institutions, and even members of the IRB.³¹ The IRB should make sure that the injury statement conforms to the language in the contract with the site. The contract will likely contain specific methods for allocating liability to the sponsor or the institution at which the research is being conducted. This process, although essential to describe before the trial is initiated, is of little concern to the research participant and should not be included in the consent form. Trials sponsored by the pharmaceutical industry are more likely to offer coverage for medical expenses resulting from a research-related injury than those supported internally or through government funding.³² Injury statements tend to be written at a higher level than other portions of the consent and few meet the Institute of Medicine guidelines for compensation for research-related injuries.³² Injury statements may contain wording that waives or appears to restrict the rights of the participant to receive treatment for research-related injuries. Language is sometimes included that places a certain level of responsibility on the research participant, such as, ‘if you followed your doctor’s instructions’ or ‘if you followed all study-related procedures.’ In some cases even the PI and the institution are included through further modifications such as ‘procedures that were properly performed’ Since study participants do not give up their rights to pursue a legal remedy in the event of an injury, it is unclear why these apparent restrictions appear in the consent form, except to inhibit participants from reporting problems. The language is so vague that study participants might feel that they have no recourse for treatment as a result of a missed appointment or failure to complete a study procedure. While all involved in the research enterprise are concerned about potential liability, the risks assumed by research participants are real and are usually accepted with no guarantee of benefit.

Qualifications of the investigator and investigative team

Patients expect that the clinical care they receive will be provided by physicians, nurses, and other health professionals who are qualified to deliver these services. Clinical researchers must meet this standard and fulfill other

obligations to the sponsor, regulatory authorities, and IRBs. The significance of the additional obligations relates to the protection of study participants and the credible use of new drugs or devices in future patients. Stated another way, the research team must be committed to patient care and scientific integrity. Ultimately one individual at the site is responsible for meeting these commitments – the PI.

The process by which the IRB determines that an investigator is qualified to conduct a clinical study relates to their ability to meet criteria established by the IRB, the institution hosting the research, the sponsor, and regulatory authorities. Investigator responsibilities are outlined in the ICH E6 *Guideline for Good Clinical Practice* and in an FDA *Guidance for Industry*. The IRB needs evidence that the PI (usually a physician, podiatrist, or dentist) is capable of providing the medical care required by the study and can facilitate access to specialists in the event of a Serious Adverse Event (SAE). Evidence for this typically comes from the investigator's curriculum vitae. If the investigator is expected to perform a procedure as part of the research, the IRB may seek evidence that the investigator is authorized by the institution to carry out the procedure. Most IRBs will require the investigator to submit an FDA 1572 form or clinical trial agreement to demonstrate that the investigator intends to fulfill commitments made to the sponsor, and agrees to permit the sponsor and regulatory authorities access to records assuring adherence to the study protocol and to verify data collected during the study. Investigators will need to establish that they have received training in the conduct of human research and that it is in date. The IRB will usually ask the investigator to identify the total number of trials in which they are participating, the number of participants enrolled, and personnel who will be committed to the trial. Additional discussion of investigator qualifications can be found in Chapter 4.

Risk–benefit analysis

One of the first decisions made by the IRB chairperson, or designee, is determining the level of risk associated with the proposed research. Occasionally, industry sponsors are interested in de-identified data extracted from medical records, which could qualify for an exemption from IRB review. Examples of these kinds of studies include retrospective evaluations of prescribing patterns for certain conditions, or a meta-analysis of existing data. The FDA regulations are silent with regard to exempt research related to drug or device studies, except for the special case where emergency use of a drug or device is required. In the USA, adherence to HIPAA regulations is required and can influence the manner in which data is collected.

Prospective studies that are found to be of minimal risk may qualify for expedited review and approval. Minimal risk is defined in these terms: 'the probability and magnitude of harm or discomfort anticipated in the research

are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations or tests.’ Differences in interpretation of ‘minimal risk’ can result in vastly diverse determinations among IRBs. This is particularly true in the application of the FDA standards for research involving children.³³ Some kinds of survey research might lead to the identification of issues that clearly are not minimal risk.³⁴ The difficulties encountered in applying the minimal risk standard have resulted in some IRBs abandoning this category in favor of a full board review for all prospective studies.

Most drug or device research exceeds minimal risk and requires full board review. The criteria for IRB approval of FDA-regulated research are found in Table 8.5. While the criteria are clear and succinct, problems with approval can occur because each ethics committee, consciously or unconsciously, develops a working definition for words such as ‘minimized,’ ‘benefits,’ ‘risks,’ ‘equitable,’ ‘reasonable,’ ‘appropriate,’ and ‘adequate.’

Furthermore, even within the committee definitions can and do change from protocol to protocol depending on the drug or device being evaluated, the research team, the research location, the condition under study, and the population being studied. Better consistency within and among IRBs could be achieved if the words mentioned above could be assigned a relative value. Being able to quantify benefits and risks offers the possibility of manipulating these ‘values’ to establish whether benefits outweigh risks.³⁵ The viability of this approach related to the benefit–risk assessment for a population has been described.³⁶ While useful in the context of societal benefit–risk, it is not clear how this can be consistently applied to measure benefit–risk for individual research subjects. Being unable to quantify benefits and risks does not necessarily mean that sponsors and investigators are helpless and subject to the whims of the individual IRBs. Methods are available, although they are not always employed, that can help the IRB better understand exactly what benefits might come to participants and that the risks are appropriate and have been minimized to the extent possible. The following paragraphs, based on the FDA criteria for approval of

Table 8.5 Requirements for approval of research

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits
- Selection of subjects is equitable
- Informed consent will be sought
- Informed consent will be documented
- Where appropriate, adequate provisions for data monitoring to ensure subject safety
- Where appropriate, adequate provisions to protect subject privacy and confidentiality
- Adequate safeguards to protect the rights and welfare of vulnerable subjects

research, describe what sponsors and investigators can do to educate IRB members and facilitate the review process.

Risks to subjects are minimized

The first step the sponsor and investigator can take is to identify all the risks and inconveniences associated with participating in the protocol. Most often the identification of risks is restricted to those related to the drug or device under investigation. While the IRB, the sponsor, and investigator might consider the investigational intervention the most important risk, as discussed above it is only one of the risks and inconveniences associated with the protocol. Once all of the risks are identified, the sponsor and investigator can facilitate the IRB review process by making a candid assessment of risks that the participant would experience as part of routine care, and those that are solely related to the research. Some risks undoubtedly result from research, such as use of placebo, surveys, and additional blood sampling; others might be less clear. If two radiographs are standard of care, are three? Some studies do not permit the use of medications that are considered as standard of care and investigators will implement a washout period in order to qualify patients for the study. Have the risks of withdrawing effective treatments been addressed? Similar considerations need to be given to every aspect of the protocol, including the amount of blood being drawn over the course of a study and the number of office visits.

Once all the risks have been identified, the sponsor and investigator can begin to address how these risks have been minimized. The specifics of how risks have been minimized will vary according to the research, but fall into three broad areas: selection and qualification of study participants, study-related methods and procedures, and monitoring and follow-up. Ultimately the sponsor can facilitate the review process by demonstrating how the protocol selects participants appropriately, and avoids enrolling individuals who are at higher risk of experiencing an AE; how study visits and procedures are scheduled to coincide as much as possible with usual clinical care activities; and for those risks that cannot be entirely eliminated, that appropriate monitoring methods have been included to reduce AEs. As local investigators usually will not have the insight to answer questions about how the protocol was developed, the sponsor should provide this information.

Risks to subjects are reasonable in relation to anticipated benefits

This is the only requirement for approval that mentions potential benefits to research participants. Most drug and device protocols are quite explicit regarding potential risks; however, potential benefits often are not discussed. The ICH E6 *Guideline for Good Clinical Practice* states that the IB should present information ‘that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk–benefit assessment of the appropriateness of the proposed trial.’ Often the background provided in the

study protocol does not convey any of the benefits that might be expected to the individual or society through the development of the drug or device. The sponsor has the best insight as to the potential benefits and should include their thinking on these. Regulations require that the available information allow an ‘unbiased risk–benefit assessment.’ While omission of any assessment by the sponsor of benefits versus risks will permit an unbiased assessment, it may also result in an assessment that is not fully informed. The IRB makes the final determination on what risks are reasonable in relation to possible benefits, and is free to ignore the assessment of the sponsor.

Selection of subjects is equitable

The purpose of equitable subject selection is to ensure that the risks of research are spread out over the groups of individuals who are expected to benefit from the findings – the principle of justice described in the Belmont Report. Both the sponsor and local investigator need to be involved in meeting this goal. The local IRB will scrutinize eligibility criteria and recruitment methods as part of fulfilling this requirement, but can only influence recruitment at the institutional level. Sponsors can help by providing information about other sites involved in multicenter trials to show their efforts in distributing risks.

Informed consent will be sought

Merely providing an informed consent template is insufficient. As recently published articles point out, informed consent is a process; there is an over-reliance on the consent form itself; and methods for assessing participants’ understanding of the risks, benefits, and their responsibilities are largely inadequate.^{37,38} Despite all the details given in the sponsor’s protocol for study-related procedures, little is routinely provided to the research team concerning the sponsor’s expectations for the timing and process of obtaining informed consent. Ultimately, the local IRB is responsible for ensuring that appropriate methods are used to obtain consent. Even so, sponsors can assist in meeting this important obligation to research participants.

Informed consent will be documented

Again, over-reliance on the consent document is frequently observed. Investigators need to document not only that consent was obtained, as evidenced by the signed consent form, but also that the process, timing, and circumstances surrounding consent are documented in the medical record. The record should reflect any questions asked by the participant, how they were answered, and the methods used by the investigator to determine the participants’ comprehension of each of the informed consent elements. Sponsors can take an active role in achieving this goal through investigator training and by providing forms or checklists to assist investigators in documenting the consent process.

Where appropriate, adequate provisions for data monitoring to ensure subject safety

As with other sections of a sponsored research protocol, great detail is provided related to AEs and how they should be reported to the sponsor. Care is taken to clearly discriminate between what will be considered a side-effect of the drug from those events that will be attributed to the underlying disease. Reporting requirements for the local investigator are outlined, and study monitors make frequent site visits to assure that reports are accurate and submitted in a timely fashion. What is often missing, but is of major importance to the IRB, is a discussion of how these reports will be handled once they are received by the sponsor. This is especially true for multicenter trials, where AEs may find their way to the site investigator and eventually to the IRB weeks or months after they have occurred. IRB members understand that instant access to AEs or unanticipated problems is unrealistic; but they would like some assurances that a process is being followed that will assist them in protecting research participant enrolled at their institution. This process is usually omitted from the clinical trial protocol. Lacking any information, the IRB is likely to assume that there is no plan to look at adverse and unanticipated events in a timely manner. This raises questions that the sponsor must answer, resulting in delays in starting the study. The process for handling these occurrences should be described in some detail. It is useful for the sponsor to include rules that site investigators can employ to determine whether a study participant should be removed from the trial. Similarly, a schedule for assessing all reported events and disseminating this information to investigators and IRBs will allay some concerns.

As discussed by Silverman, not every trial will require a Data Safety Monitoring Board (DSMB).³⁹ At the same time, a protocol mentioning that a DSMB will be constituted is of little value to the IRB. It is more important for the sponsor to provide a timeframe for the constitution of the DSMB and to share the plan developed by the board for interim analyses, stopping rules, and other patient safety issues. Timely submissions of DSMB reports to the IRB provide evidence that the sponsor and DSMB members are taking participant safety seriously. Unfortunately, some reports come to the IRB merely stating that the DSMB has met and decided that the trial should continue. This information is useless to the IRB. DSMBs should provide some assessment of the total number of study participants enrolled, the rate of study enrollment, the frequency of study violations and deviations, and an acknowledgement that AEs were reviewed, in addition to the decision to continue the study.

Where appropriate, adequate provisions to protect subject privacy and confidentiality

One of the underlying premises of medical research is the hope that the results will be generalizable, and offer society improved methods for the

identification, understanding, treatment, and prevention of disease. To achieve this goal, health information from hundreds or thousands of individuals is combined, and distilled to provide innovative therapies. Researchers and sponsors have a responsibility to protect the health information of an individual. Inadvertent disclosures of health information potentially can affect the individual's ability to obtain a job or health insurance, or could otherwise stigmatize the individual in the community. In the USA, HIPAA regulations require that individuals be told how their health information will be used, for how long it will be made available, and who will have access to it. Since its implementation, investigators have identified HIPAA disclosure as another barrier to research recruitment for all kinds of research.^{40,41} Furthermore, sponsors and investigators may need to make changes to the research plan in order to remain compliant with the rule.⁴²

Two other issues that IRBs deal with regularly relate to HIV testing and screening for drugs of abuse. Laws related to HIV testing vary according to jurisdiction. Some states require pre- and post-test counseling and may require the use of a separate consent form. Sponsors have an understandable interest in making sure that participants enrolled in a trial are not using drugs of abuse. Not only might illegal drug use confuse the results of the study, but these participants may, at least in theory, expose the sponsor to additional study costs and liability. Since recreational drug use is illegal in most countries, collecting and documenting this illegal activity may expose the individual to prosecution and legal sanctions. In order to protect study participants, IRBs may require that the sponsor obtain a certificate of confidentiality.

Adequate safeguards to protect the rights and welfare of vulnerable subjects
Children, prisoners, pregnant women, the handicapped, and mentally impaired individuals are widely considered as vulnerable to exploitation in research. Special protections are given to these populations through 45 CFR Part 46 Subparts B, C, and D and to children in FDA-regulated research through 21 CFR Part 50 Subpart C. The ICH E6 *Guideline for Good Clinical Practice* expands the definition of vulnerable groups by including those who have a subordinate role in a hierarchical structure, such as students, employees, or members of the armed forces. Many of the potential problems involving vulnerable subjects can be dealt with through modifications of the eligibility criteria. When this cannot be done, the process of informed consent will fall under closer scrutiny. Consent procedures for vulnerable populations are fully addressed in Chapter 3.

Continuing review

DHHS, FDA, and ICH guidelines each require that the IRB 'should conduct continuing review of each ongoing trial at intervals appropriate to the degree

of risk to human subjects, but at least once per year.’ At the time of first approval, the IRB should determine how frequently the research should be reviewed for reapproval. The one-year interval is commonly applied to most research; however, early-phase drug or device studies may need to be resubmitted at three- or six-month intervals. Some investigator-initiated research or research using innovative therapies where risks are unknown may need to be reported to the IRB on a case-by-case basis. Continuing reviews address a wide range of issues including the number of participants enrolled and their demographics, AE reporting, the need for changes to the informed consent document, and a literature review to show that the research question being addressed is still important.⁴³ IRBs are at some disadvantage when multicenter trials are subjected to continuing review in that the committee usually does not have access to the totality of information available to the sponsor. Generally, their review will be based on the participants recruited at their site, which may or may not reflect the experience in the entire trial. Some sponsors facilitate the review process by providing local investigators with regular updates regarding enrollment and summaries of AEs. Despite the importance of the continuing review process, IRBs are frequently cited for failing to provide adequate continuing review of research.⁴⁴

Final thoughts

Investigators and sponsors often experience frustration in dealing with local IRBs. Although some IRBs appear to have the mission of blocking clinical research, this is rarely the case. Sponsors, investigators, and IRB members each work to meet regulatory mandates and ‘follow the rules.’ Unfortunately, the rules are not always very specific and sometimes seem to come from different games. The sponsors’ chances for success are improved by selecting investigators who have established relationships with their local IRB and understand the information that is needed to assure a timely and thorough review.

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