What You Need to Know to Live in Harmony With Your Institutional Review Board (IRB)/Research Ethics Committee (REC)

Institutional review board (IRB), independent ethics committee, research ethics committee (RECs), and ethical review board are all names for a formal group dedicated to reviewing, monitoring, and approving research with the goal of protecting the rights and welfare of human subjects. In the United States, the National Research Act was passed in 1974 by Congress and required the establishment of IRBs for research involving human subjects. In Europe, the concept for the creation of these bodies was first introduced in the 1975 revision of the Declaration of Helsinki, which proposed that the protocol for all clinical trials be reviewed by an “independent committee” before initiation of the study. These groups have been developed to protect human subjects in research studies. This chapter reviews the IRB/REC mission and provides practical information for working with your IRB/REC.

Duties of IRBs/RECs

The purpose of ethics committees is to protect human subjects involved in research (separate ethics committees exist to protect animal subjects involved in research). The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines have recommendations regarding IRBs and RECs. The ICH GCP Guidelines are discussed more fully in a later chapter, but below is a summary of the Guidelines with respect to ethics committees.

As per the ICH GCP Guidelines, the ethics committee should review and approve the following documents:

- research protocol(s)/amendment(s);
- written informed consent document(s) and document revisions;
- subject recruitment procedures (eg, advertisements);
- written information to be provided to subjects;
- investigator’s brochure;
- available safety information;
- information about payments and compensation available to subjects;
- investigator’s current curriculum vitae and/or other documentation evidencing qualifications; and
- any other documents that the IRB/REC may need to fulfill its responsibilities.

The ICH GCP Guidelines state that reviews should take place within a reasonable time period, and that IRBs/RECs should provide their views (approval, disapproval, needed modifications) in writing. Furthermore, the responsibilities of the IRB/REC do not stop once the protocol is approved and the first subject is enrolled. Instead, the IRB/REC must periodically review the protocol and other documents related to the trial at intervals appropriate to the degree of risk to the human subjects, but at the least, once per year. It is the responsibility of the principal investigator to report to the IRB/REC
any deviations from or changes to the protocol, all adverse drug reactions that are both serious and unexpected, and any new information that may adversely affect the safety of subjects or the conduct of the trial. The ICH GCP Guidelines, as well as the United States FDA Code of Federal Regulations, state that IRB/RECs should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available to regulatory authorities as needed (also see 45 CFR 46.115; 21 CFR 56.115).

The ICH GCP Guidelines also recommend that each IRB/REC consist of at least 5 members, 1 of whom has nonscientific primary areas of interest, and 1 of whom is not part of the institution or trial site. Decisions about a particular trial should only be made at meetings where at least a quorum is present and only those members who participate in the review and discussion about a particular trial should be allowed to vote or express an opinion about that trial. Each of the regulatory agencies below has based their own procedures on the ICH GCP Guidelines but each country maintains authority for their specific review process, and even within countries there may be regional/provincial differences in procedures.

**Regulatory Oversight**

**United States**

IRBs, as they are commonly referred to in the United States, are mandated by the federal government as part of the Code of Federal Regulations (CFR) (Part 46 [Protection of Human Subjects] of Title 45 [Public Welfare] and FDA regulations on IRBs at 21 CFR 56). These regulations cover research that is both federally funded (Title 45 Part 46) and FDA-regulated (21 CFR 56). Institutions that either receive federal research dollars or conduct FDA regulated research must comply with these regulations. The Office for Human Research Protections (OHRP) of the United States Department of Health & Human Services regulates IRBs that review federally funded research. The FDA has its own section that has oversight over IRBs that review FDA-regulated research. In some instances, institutions voluntarily grant jurisdiction to OHRP to review privately funded FDA-regulated research; as a result many IRBs are regulated by both the OHRP and FDA.

“The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research.”

--US Food and Drug Administration (FDA) 2007

The United States system has allowed for the formation of different types of IRBs. The most familiar are those associated with universities and hospitals, which are called local IRBs. In addition, many IRBs today are not for profit or for-profit organizations. Labeled as external, central or independent IRBs, these organizations are governed by the same regulations and have the same responsibilities as local IRBs. Using an external IRB frees up the staff of the institution and may resolve some conflicts of interest; however, other conflicts of interest may arise because these organizations are sometimes paid by the study sponsor.

A concern by the public about the lack of credibility and consistency among IRBs regarding the protection of human subjects prompted the formation of the Association for the Accreditation of Human Research Protection Programs (AAHRPP) in 2001 as a private nonprofit organization established to promote excellent and ethically sound research. A number of IRBs have elected to pursue voluntary accreditation by the AAHRPP. In addition to accrediting institutions in the United States, the AAHRPP has also accredited institutions in Canada, Korea, and Singapore.
Member states of the European Union subscribe to the Directive on Clinical Trials, which was proposed in 2001 and mandates the establishment of research ethics committees (RECs). The recommendation is purposely vague, however, and each member state has adopted its own regulations regarding RECs. For example, Sweden has 6 regional RECs and 1 central committee, which serves as an appeal board for cases that are either rejected by 1 of the 6 regional RECs or in situations where a regional REC is indecisive. In Hungary, a central Clinico-Pharmacological Ethics Committee decides on all pharmaceutical research protocols involving humans. In addition, each institution must have its own Institutional Ethics Committee that monitors trials and decides whether resources are adequate for the particular study. In the United Kingdom, RECs are recognized by the United Kingdom Ethics Committee Authority (UKECA), which consists of the Secretary of State for Health, the National Assembly for Wales, the Scottish Ministers, and the Department of Health. These recognized RECs then review applications for clinical trials and can be broken down into 3 categories: 1) those that review phase 1 studies in healthy volunteers throughout the UK, 2) those that review trials that take place at sites within a specific geographic region, and 3) those that review trials that are other than phase 1 trials in healthy volunteers throughout the United Kingdom.

“A clinical trial may be initiated only if the Ethics Committee ... comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.”

--Directive 2001/20/EC

In Japan, ethics committees were established at all of the medical schools and many general hospitals initially independent of government oversight. Two types of ethics committees exist in the Japanese system: 1) one that reviews and monitors drug clinical trials (called a chiken-shinsa-iinkai), and 2) one that reviews protocols from investigators affiliated with the institution (called a rinri-iinkai). The first type is regulated by the Ministry of Health, Labor, and Welfare. The latter type is comprised primarily of self-governing bodies that are not regulated by the government.

Composition of IRBs/RECs

In the United States, the composition of an IRB is described in the Code of Federal Regulations (45 CFR 46.107; 21 CFR 56.107). As per the ICH GCP Guidelines, each IRB must have at a minimum 5 members with varying backgrounds who are “sufficiently qualified” through experience and expertise. Diversity in race, gender, and cultural backgrounds is also strongly suggested. Furthermore, the IRB must be sensitive to community attitudes and knowledgeable about the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. Each IRB must contain at least 1 member whose primary concerns are scientific, 1 member whose primary concerns are nonscientific, and 1 member who is not affiliated with the institution where the research is being conducted.

The European Union Directive on Clinical Trials has stated the minimum requirements for RECs in member states. Specifically, each REC should be an independent body within the individual member state, and it should consist of both healthcare professionals and nonmedical members. Each member state dictates its own additional requirements. For example, in Sweden, regional RECs have 10 members, including 5 lay members who represent the public; but in Portugal, each REC has 7 members composed of one of each of the following: medical doctor, nurse, pharmacist, jurist, theologian,
psychologist, and sociologist.

The Japanese system also prescribes diversity within its ethics committees. A recent study on Japanese ethics committees at medical schools and general hospitals showed that these committees consist of both men and women, as well as outside members unaffiliated with the facility. Although the majority of members were physicians and other healthcare professionals, legal advisors, ethics professionals, and people involved with other humanities have also been included.

*Interacting With Your IRB/REC*

The interrelationship between the investigator, sponsor, and IRB/REC is complex. Generally, the investigator, and not the sponsor, is the entity that maintains contact with the IRB/REC, and is responsible for maintaining all correspondence to and from the committee. Once you have made the decision to be the principal investigator of a clinical research trial, one of the first things you should do is contact the IRB/REC (either internal or external) that will be responsible for reviewing the study materials to learn its procedures and timelines. Generally these procedures and timelines can be found on your IRB’s/REC’s website. Although the general approach of each IRB/REC will be similar because of regulatory guidelines, each will have specific forms and requirements that must be used and followed for the research to be reviewed, and ultimately approved.

The process may take weeks to months, depending on the workload and staffing of the IRB/REC, as well as the type and complexity of the research. The majority of IRBs/RECs meet on a specific schedule. Some request a letter of intent before the actual submission, so that review of the submission can be accommodated into established timetables. A fee is generally required but there may be exceptions for some investigator-initiated research and some government (eg, National Institutes of Health) or nonprofit (eg, International Psoriasis Council) sponsored projects.

As mentioned with respect to ICH GCP Guidelines, a complete submission package usually consists of an IRB-specific application, a protocol narrative, including recruitment processes, how adverse events will be reported, the informed consent document, relevant safety information (eg, investigator’s brochure, package insert), and any advertising or study-related materials. It is important that the protocol is written so that it is understood by both the scientific (medical experts) and nonscientific (lay) members of the board. The submission, however, must provide sufficient detail to explain the justification for the study and the research plan, so that the reviewers can determine the risks and benefits of the research and if it has statistical validity (ie, sufficient power), to either approve or disapprove the study.

Some institutions or sponsors require the principal investigator, study coordinator(s), and possibly others involved in the conduct of the study to complete a course on protecting human subjects, proper documentation, and specific research techniques before any studies can be initiated. Most institutions will accept on-line training to meet this requirement. Disclosure and review of the financial relationships of the principal investigator, subinvestigators, study staff, and his/her clinic or laboratory may also be necessary.

The IRB/REC may request modifications to any of the submitted materials, including the protocol, informed consent forms, recruitment materials and data recording documents. Additional protections may be requested for special subject populations, such as children, prisoners, and individuals with diminished mental capacity.
Tips

Some tips for maintaining a good relationship with the IRB/REC include taking criticism constructively, and responding promptly, clearly, and politely to any additional IRB requests or questions. Responses should be easy to understand and relate to the original comments by the IRB/REC, and should be transmitted in the format most preferred by the IRB/REC (eg, track changes). Page numbers should be included on both the original submission package and modifications, with changes underlined or highlighted. The easier you can make the review process for them, the faster they are likely to respond. Lastly, let the IRB/REC staff know how much they are appreciated - their work is important to maintaining the welfare of subjects.

Conclusion

IRBs/RECs perform a significant task: to protect those persons who have graciously volunteered to participate as human subjects in research experiments. Although the creation of these ethics committees is generally mandated by federal regulations and international guidelines and directives, the specific composition and processes are unique to each country and institution. Thus, as an investigator, you should familiarize yourself with the regulations governing clinical research along with the specific process of your respective IRB/REC before deciding to participate in a particular study. It is in your best interest and the best interest of the study to follow your IRB/REC guidelines and present a submission package that is complete and easy to understand. Finally, it is important to remember that although IRBs/RECs provide ethical safeguards, you, the investigator, are ultimately responsible for the safety and welfare of the subjects and the conduct of the trial.

Resources


