

How to Do Human-Subjects Research If You Do Not Have an Institutional Review Board

Todd W Rice MD MSc

Introduction

Institutional Review Boards and Their Roles

Human-Subjects Research

Options for Investigators at Institutions Without IRBs or Ethics Committees

Start an Institutional Review Board

Use a Commercial IRB

Partner With an Institution That Has an IRB

Informed Consent

Summary

Biomedical research with human subjects has expanded outside of traditional medical centers and hospitals into other health care entities, such as rehabilitation facilities, free-standing out-patient treatment centers, and even home-health agencies. Regardless of the location, federal regulations mandate that all human-subjects research must be overseen by an institutional review board (IRB) or ethics committee to ensure the research abides by the Code of Federal Regulations. Consequently, all human-subjects research must be reviewed and approved by an IRB prior to initiation of any research procedures. Unfortunately, many of these nontraditional research facilities do not have easy access to an IRB. This does not render such research exempt from federal oversight. Clinicians at these facilities have viable options for obtaining IRB approval and legally conducting such research. This paper outlines the available options and their pros and cons. *Key words: ethics, institutional review board, IRB, human-subjects research; non-academic health care facilities.* [Respir Care 2008;53(10):1362–1367. © 2008 Daedalus Enterprises]

Introduction

Almost all academic medical centers have their own institutional review boards (IRBs), because one of their main missions is to conduct research. Many non-academic

medical centers and hospitals have their own IRBs, as well, especially if they frequently conduct research. However, with the expansion of home-health agencies, out-patient treatment centers, and rehabilitation facilities, health care is increasingly being provided through less traditional, and often less organized, means. Many of these health-care institutions do not have their own IRBs. Nonetheless, more and more of the employees at these institutions desire to conduct human-subjects research. All human-subjects research must be overseen and reviewed

Todd W Rice MD MSc is affiliated with the Division of Allergy, Pulmonary, and Critical Care Medicine and the Vanderbilt Institutional Review Board, Vanderbilt University School of Medicine, Nashville, Tennessee.

Dr Rice presented a version of this paper at the RESPIRATORY CARE Journal Symposium at the 53rd International Respiratory Congress of the American Association for Respiratory Care, held December 1-4, 2007, in Orlando, Florida.

The author reports no conflict of interest related to the content of this paper.

Correspondence: Todd W Rice MD MSc, Division of Allergy, Pulmonary, and Critical Care Medicine, T-1218 MCN, Vanderbilt University School of Medicine, Nashville TN 37232-2650. E-mail: todd.rice@vanderbilt.edu.

by an IRB, regardless of whether the institution has its own IRB. This paper describes the importance of an IRB and discusses 3 options for IRB oversight and approval for research by personnel at institutions that do not have their own or easy access to another institution's IRB.

Institutional Review Boards and Their Roles

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research proposed Title 45, Part 46 of the Code of Federal Regulations, widely known as the Common Rule, which was signed into law in 1981. These federal regulations require that all human-subjects research funded by United States federal money be conducted under the oversight of the Office for Human Research Protections.¹ The local IRBs, which are overseen by the Office for Human Research Protections, are charged with protecting the rights, safety, and welfare of human subjects in research activities under the auspices of an institution to which the IRB has an affiliation. In fact, the requirement for IRB oversight now extends to all human-subjects research, regardless of the funding, supporting, or designing source, so all human-subjects research must be reviewed and approved by an IRB registered with the Office for Human Research Protections² before any research procedures, including eligibility screening, can be performed with human subjects in the United States. Since these regulations derive from federal legislation, it is illegal to conduct any human-subjects research procedures without first obtaining approval from an IRB or other appropriate ethics committee (such as an institutional ethics committee, research ethics committee, or ethical review board). The penalties for doing so may be severe, ranging from monetary fines to the individual and/or the institution to imprisonment. In addition, most journals have adopted the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, as put forth by the International Committee of Medical Journal Editors.³ These requirements necessitate an indication that the research procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.⁴ To fulfill this requirement, most journals now require a statement in every submitted manuscript that approval was obtained from the IRB, or equivalent entity, prior to initiating the research. Some journals even request a copy of the IRB determination prior to considering any submitted manuscript. If IRB approval was not obtained, the journals refuse to even consider the manuscript.

The IRB (or similar research ethical review entity) reviews proposed research and has the authority, granted by the federal regulations and local institutional policy, to approve, disapprove, or require modifications to all hu-

man-subjects research prior to research initiation. In this role the IRB assumes numerous duties and often must collaborate closely with other institutional bodies, including scientific review committees, human-subject radiation committees, biosafety experts, conflict-of-interest committees, and requested ad hoc expert reviewers. Despite all IRBs abiding by the same federal regulations, individual IRBs often have local restrictions or different interpretations of the federal regulations. This results in some different determinations by different IRBs, depending on locale.⁵⁻⁸ IRBs also bear the responsibility of reviewing ongoing research at least annually to re-evaluate the risk-to-benefit assessment and ensure that the research continues to be conducted according to the regulations. To abide by the regulations, investigators and other research personnel require education and training, which also lies under the domain of the IRB.

Human-Subjects Research

The Common Rule (Title 45, Part 46 of the Code of Federal Regulations) regulates human-subjects research. Projects that qualify as either not research or research that does not involve human subjects do not fall under the purview of the Office for Human Research Protections. Technically, that means that these projects are not subject to IRB oversight. However, this differs according to location. Many institutions still require IRB review of both non-human-subjects research and non-research projects, to ensure that they meet the criteria for those types of projects and really do not fall under the federal guidelines for human-subjects research. To accomplish this, IRBs and investigators must first determine whether the proposed activity involves research, and, if so, whether the research involves human subjects. The Web site of the Office for Human Research Protections provides a flow chart to help determine whether a project requires oversight.⁹

Research is defined as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."¹⁰ Several key criteria in that definition must be met to qualify as research. For example, a case report is often not considered a "systematic investigation" and therefore may not require IRB approval. However, many journals request that the person who is the focus of the case report provide informed consent for the publication of the case.

Quality-assurance/quality-improvement projects are another example. These are undertaken to improve the quality of care at a local institution, so they do not meet the criterion of "contributing to generalizable knowledge."¹⁰ However, if the results are published in a journal, then they do contribute to generalizable knowledge. Therefore, any "quality-assurance" project conducted with the intent of publishing the results should be submitted for IRB re-

view and approval prior to initiating the project. On the other hand, quality-improvement projects undertaken with the sole intent of improving local care do not require IRB approval. If, once the results are known, the decision is made to publish the data because it may be useful for others outside of the local institution, then the project would require IRB approval at that time. These quality-improvement projects are the only situation in which an IRB can approve a project after it has already been started or completed, and in these cases the IRB is actually approving the dissemination of the data for generalizable knowledge rather than the project itself. Similar to quality-assurance projects, data obtained for training or teaching purposes is also not meant to contribute to generalizable knowledge and does not qualify as research. However, these projects need IRB approval before they can be published.

The regulations define human subjects as “living individuals about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.”¹⁰ Similar to the definition for research, several key phrases shape the interpretation of this regulation. Some studies do not qualify as human-subjects research because they do not meet the criteria. An example of this is research that uses data or specimens that are completely de-identified of all private health information, as defined by the Health Insurance Portability and Accountability Act. There are subtle nuances in the determination of whether data are completely de-identified. For example, age is allowed (as long as specific ages ≥ 90 y are not recorded), but date of birth is not. In fact, all dates represent identifiable data. Therefore, date of admission or date of surgery would be not be allowed in data that were intended to be entirely de-identified. Likewise, geographic identifiers smaller than a state are also considered identifiable information. Because of these nuances, many institutions require confirmation from the IRB that the data (or specimens) used in these projects meet the definition of non-human-subjects research and do not utilize identifiable private information. Other projects that are considered non-human-subjects research include those that use only anonymously returned questionnaires, publicly available databases, such as the Medicare database, and projects that use non-living subjects, such as cadavers. It should be noted that many institutions have strict criteria for projects that can utilize cadavers, to ensure privacy and respect for the deceased.

Options for Investigators at Institutions Without IRBs or Ethics Committees

Since the federal regulations require that all human-subjects research is overseen by an IRB or ethics committee, regardless of where that research is conducted, inves-

tigators at institutions without IRBs have only 3 options: not to conduct research or to limit studies to those that can be classified as “non-research” or “non-human subject,” or to find an IRB or ethics committee to review and approve their projects.

In addition to conducting projects that qualify as either non-human-subject research or not research, investigators at health care institutions that lack an IRB can also conduct human-subjects research, but it takes some additional effort. All human-subjects research conducted in the United States must be overseen and approved by an IRB or ethics committee. For an investigator at an institution that has an IRB, this means simply submitting the proposed study to the IRB for review and approval. Investigators at an institution without an IRB still need to obtain approval from an IRB before initiating a study. There are 3 options (Table 1):

- Start an IRB at their institution
- Use an external, commercial IRB
- Partner with another institution that has an IRB and is willing to serve as the IRB of record for the study

Start an Institutional Review Board

Any health care institution can have its own IRB, regardless of how much research is done at that institution or whether the institution is affiliated with a medical center, has research as one of its missions, or is an academic institution. To start an IRB, an institution must submit 2 forms to the Office for Human Research Protections (both of which can be found on that office’s site²) plus a Federal-Wide Assurance, which is a document that outlines IRB rules and regulations and commits the IRB to following those rules and regulations and to oversight by the Office for Human Research Protections. Starting and maintaining an IRB takes substantial money, time, and manpower. An IRB must have a designated institutional official (though that person does not have to be exclusively assigned to the IRB) and a human protections administrator, plus at least 5 IRB members, one of whom serves as the chair of the committee.¹¹ The IRB committee has to have at least one scientist, one non-scientist, and one member who is not affiliated with the IRB’s institution. To obtain a Federal-Wide Assurance, training modules must be completed by the designated institutional official, the human protections administrator, and the IRB chair, and the institution must have written policies and procedures for how the IRB will operate.

In addition to not usually costing the investigator anything, having its own IRB also has some important advantages to a local institution. The local IRB is able to review

HOW TO DO HUMAN-SUBJECTS RESEARCH IF YOU DO NOT HAVE AN INSTITUTIONAL REVIEW BOARD

Table 1. Options for Obtaining IRB Approval at a Facility Without an IRB

Strategy for Obtaining IRB Approval	Pros	Cons
Start own IRB	<ul style="list-style-type: none"> Studies reviewed on site Can “outsource” IRB to other facilities; collaboration The IRB will understand local customs and standards of care The speed of the review is locally controlled IRB members and investigators become familiar with each other and common research techniques 	<ul style="list-style-type: none"> Requires Federal-Wide Assurance and registration with Office for Human Research Protections Requires IRB team and IRB members (at least 5) Requires written IRB policies and procedures Requires expert representation for each research area Expensive Requires substantial institutional/facility support Time-consuming May only be needed for a few studies a year
Contract with commercial IRB	<ul style="list-style-type: none"> Large number of choices Can change to another IRB in future projects Easy to work with Rapid review of research Can be used for any number of studies (one to hundreds per year) External IRB provides expert reviewers 	<ul style="list-style-type: none"> Expensive May not be familiar with local practice and customs Researcher’s facility may still need Federal-Wide Assurance Researcher’s facility still needs policies for reviews, reporting of adverse events, etc IRB members and investigators may not be familiar with each other and common research techniques
Coordinate with institution that has an IRB	<ul style="list-style-type: none"> The IRB will usually understand local customs and standards of care Facilitates collaboration, even beyond IRB activities Relatively inexpensive Convenient 	<ul style="list-style-type: none"> Requires memorandum of understanding/contract with IRB institution Researcher’s institution may still need Federal-Wide Assurance Speed of review externally controlled IRB members and investigators may not be familiar with each other and common research techniques May need research liability insurance

IRB = institutional review board

all studies that occur at that institution. This is especially important for institutions that have more than one investigator or more than isolated studies. The IRB can also serve as the IRB for other local institutions that lack an IRB, which might defray the costs of maintaining the IRB over time. There are other advantages of having a local IRB. The regulations on oversight of human-subjects research delineate that the language in the consent form should be appropriate for the educational level of the local population, customs, and traditions. Furthermore, since “standard of care” is determined by the routine care provided locally, a local IRB is much more likely to understand the local standards of care that would not be considered procedures done for research purposes only. Instead of relying on another IRB to meet, having an IRB at the institution would also allow control over the timing of the reviews and the development of familiarity between the IRB reviewers and the investigators. This may be especially helpful if an investigator is using the same research procedure (or, for example, questionnaire) in multiple studies, since the IRB would be familiar with the procedure and not have to “re-invent the wheel” for each subsequent submission.

Having its own IRB also has some disadvantages for an institution. An IRB can be a financial burden to an institution, and the institution must maintain a designated institutional official, a human protections administrator, and its Federal-Wide Assurance with the Office for Human Research Protections via the required renewal process. These are often more burdensome than partnering with another IRB or utilizing a commercial IRB, especially if only one or a few studies are conducted annually.

Use a Commercial IRB

A commercial IRB is registered with the Office for Human Research Protections and has a Federal-Wide Assurance that allows it to oversee and approve human-subjects research. Most such IRBs are able to approve all types of human-subjects research, including both health science research and behavioral science research. Almost all such IRBs have the required expertise to review and approve studies that enlist vulnerable populations, such as children, pregnant women, prisoners, and people with impaired decision making. Since these IRBs are “for-profit,” they charge the investigator for the reviews. Commercial

IRBs exist in the United States and Canada (see <http://www.circare.org/info/commercialirb.htm>), and their fees differ. Use of these IRBs is limited to investigators at institutions that do not have their own IRBs, which are mostly non-academic health-care institutions. An investigator at an institution without an IRB is free to use any of the commercial IRBs in the same country as the research institution (because countries have some differences in regulations).

Using a commercial IRB to approve human-subjects research has advantages and disadvantages. The investigator has a choice of which commercial IRB to use, and if a commercial IRB does not provide service the investigator finds desirable (eg, too slow a review), the investigator can use another IRB for future projects. Because they are for-profit, most commercial IRBs view themselves as businesses, so they tend to be easy to work with and to provide rapid review. In addition, if an investigator uses the same commercial IRB for all of his or her studies, that commercial IRB should gain familiarity with that investigator's common research procedures, questionnaires, et cetera, which should expedite subsequent reviews.

Commercial IRBs also have some disadvantages. With a federally funded study, the local institution still needs a Federal-Wide Assurance. In addition, with researchers who conduct only one or a few studies, the commercial IRB may not be familiar with the research procedures or the local customs, traditions, or standards of care. Also, using a commercial IRB often costs the investigator money from his or her own funds.

Partner With an Institution That Has an IRB

Another means of obtaining IRB approval is to partner with an institution that has an IRB. That institution agrees to function as the IRB of record for the studies at the partnering institution. This is common when investigators from an institution that has the IRB develop a study protocol that includes outlying clinics or other health-care institutions to help them enroll subjects. The IRB at the main institution reviews the study (and may already be familiar with the study) and the consent form(s) for each participating institution. All protocol deviations and adverse events are reported to the main institution's IRB, regardless of where they occurred. This arrangement usually requires a formal agreement, contract, or memorandum of understanding between the institutions.

In addition to being cost-efficient, this sort of partnering agreement may have other benefits. Since the institutions are usually geographically close, they are likely to have similar local customs, traditions, and standards of care, so incorporating these into the review is easy for the IRB. Furthermore, the IRB may already be, or may quickly

become, familiar with the investigators at the partnering institution, which may also expedite the review, because the IRB can develop a working understanding of the research procedures and personnel. This partnership may facilitate efficiencies in both systems, referrals for care, and future research collaborations.

Forming a partnership with an institution that has an IRB is not without detriments. After finding a willing partner, which may be difficult, a formal contract or memorandum of understanding must be agreed upon. Financial details will also need to be negotiated if the IRB charges for its services. If the study is federally funded, the local institution will need a Federal-Wide Assurance. The speed of the review will be out of the control of the local institution and dependent on the IRB's practices. And, although partnering with another institution's IRB may provide familiarity between reviewers and investigators, it is still an external review and that familiarity may not be present, especially for the first few reviews.

Informed Consent

IRB review and approval is required for all human-subjects research, regardless of which of the 3 methods described above is used to obtain that review. The IRB must evaluate whether the risks to participants are minimized for accomplishing the research objectives. This requires a detailed analysis of the study design, level of expertise of the investigators, and characteristics of the research participants. In addition, the IRB must rigorously assess the proposed informed-consent process and forms to ensure that participants are able to voluntarily provide informed consent without coercion or undue influence. Informed consent is an integral part of good research practices and is one of the 3 principles established in the Nuremberg Code and one of the fundamentals set forth by the Declaration of Helsinki.⁴ Unless an IRB agrees that the study meets the criteria for waiver of consent,¹² informed consent should be obtained from all research participants prior to their taking part in the study. The consent must be obtained with an informed-consent document that has been reviewed and approved by the IRB prior to use. Once the consent form has been reviewed and approved by the IRB, it can be presented to a potential participant, who reads the document, is allotted time to ask questions (or take the document home to scrutinize), and then signs the document to verify understanding of the study and agreement to participate. The same IRB that reviews and approves the study should also review the informed consent document to ensure it is written in language understandable to the lay person and appropriate to local education, customs, and traditions. The IRB should date-stamp the consent form

with dates of approval and expiration to demonstrate that they approved it before it is used.

Summary

All human-subjects research must be overseen by an IRB or equivalent entity prior to initiating the study, regardless of whether the work is done at an institution that has its own IRB. Investigators at institutions without IRBs still must have their human-subjects studies reviewed and approved by an IRB, by either creating an IRB at their institution; using a for-profit, commercial IRB; or partnering with an institution that has an IRB. Informed consent must be obtained in all human-subjects research, unless the IRB agrees that the criteria for waiver of consent are met. The informed-consent document should be reviewed and approved by the same IRB that reviewed the study, and the study subjects must provide informed consent prior to initiating any research procedures.

REFERENCES

1. United States Department of Health & Human Services: Office for Human Research Protections (OHRP). <http://www.hhs.gov/ohrp>. Accessed August 7, 2008.
2. United States Department of Health & Human Services: Office for Human Research Protections (OHRP). Registration of an institutional review board (IRB) or independent ethics committee (IEC). October 25, 2006. <http://www.hhs.gov/ohrp/assurances/>. Accessed August 7, 2008.
3. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. <http://www.icmje.org>. Updated October 2007. Accessed August 7, 2008.
4. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2000; 284:3043-3045.
5. Dziak K, Anderson R, Sevick MA, Weisman CS, Levine DW, Scholle SH. Variations among institutional review board reviews in a multisite health services research study. *Health Serv Res* 2005;40(1):279-290.
6. Mansbach J, Acholonu U, Clark S, Camargo CA Jr. Variation in institutional review board responses to a standard, observational, pediatric research protocol. *Acad Emerg Med* 2007;14(4):377-380.
7. Vick CC, Finan KR, Kiefe C, Neumayer L, Hawn MT. Variation in institutional review processes for a multisite observational study. *Am J Surg* 2005;190(5):214-230.
8. Silverman H, Hull SC, Sugarman J. Variability among institutional review boards' decisions within the context of a multicenter trial. *Crit Care Med* 2001;29(2):235-241.
9. United States Department of Health & Human Services: Office for Human Research Protections (OHRP). Chart 1: Is an activity research involving human subjects covered by 45 CFR part 46? September 24, 2004. Available from: <http://www.hhs.gov/ohrp/human-subjects/guidance/decisioncharts.htm#c1>. Accessed August 7, 2008.
10. National Institutes of Health. Office of Human Subjects Research. Code of Federal Regulations, Title 45, Part 46. Protection of human subjects, subpart 102 (definitions). <http://www.hhs.gov/ohrp/human-subjects/guidance/45cfr46.htm#46.102>. Accessed August 25, 2008.
11. Enfield KB, Truitt JD. The purpose, composition and function of an institutional review board: balancing priorities. *Respir Care* 2008; 53(10):1330-1336.
12. Neff, MJ. Informed consent: what is it? who can give it? how do we improve it? *Respir Care* 2008;53(10):1337-1341.