

# CHEST<sup>®</sup>

Official publication of the American College of Chest Physicians



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Henri G. Colt and Ruth A. Mulnard

*Chest* 2006;130:1605-1607  
DOI 10.1378/chest.130.5.1605

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## Writing an Application for a Human Subjects Institutional Review Board\*

Henri G. Colt, MD; and Ruth A. Mulnard, RN, DNSc

**After reading this article, readers will be able to do the following: understand the role and responsibilities of an institutional review board (IRB); recognize the major areas that must be addressed in an IRB submission; and avoid common mistakes in writing a research application submission to an IRB.** (CHEST 2006; 130:1605–1607)

**Key words:** institutional review board; medical writing; research application

**Abbreviations:** FDA = Food and Drug Administration; IRB = institutional review board

**H**uman subjects institutional review boards (IRBs) were created as a direct result of ethical concerns about the preservation of autonomy, beneficence, nonmaleficence, and justice pertaining to research in human subjects. These concerns actually began during the Nuremberg trials during which medical experimentation on prisoners of war by Nazi doctors became apparent. Following the creation of the Nuremberg Code of 1945, an international code of ethics was formulated in the Declaration of Helsinki in 1964.<sup>1</sup>

In the United States, rules and regulations of the Public Health Service led to the creation of IRBs in the 1970s. Further regulations, including the Code of Federal Regulations Protection of Human Subjects (45CFR Part 46), are the direct result of various abuses of patient rights, such as those that occurred during the 30-year government-sponsored Tuskegee syphilis study, during which 300 black men with syphilis were followed up longitudinally, yet were untreated, despite the recognized effectiveness of

antibiotic treatment for this disease that had been discovered. In conjunction with the regulations under 45CFR46, are the US Food and Drug Administration (FDA) regulations under Title 21, which convey additional requirements and oversight for the protection of human subjects engaged in research that relates to food, drugs, biological agents, and devices.

According to the National Research Act Public Law 99–158 and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research,<sup>2</sup> any funded or unfunded research that involves human subjects must be reviewed and approved by an IRB, including research that is “conducted, supported, or otherwise subject to regulation, that occurs outside the United States.” The regulatory definition of the term *research* involves “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge,” while the term *human subject* means “a living individual 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.”<sup>2</sup>

In order to avoid initiating a research activity without the appropriate approvals in place, all scholarly activities could benefit from scrutiny using these definitions. Even the activity of a retrospective (or prospective) medical record chart review designed to acquire data would meet these definitions because the project is “systematic” and intends to contribute to generalizable knowledge, and involves “identifiable private information” from the medical files, which would warrant IRB review.

\*From the Department of Pulmonary and Critical Care Medicine (Dr. Colt), and the Institute for Brain Aging and Dementia (Dr. Mulnard), University of California, Irvine, Irvine, CA.

The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Manuscript received August 17, 2006; revision accepted August 21, 2006.

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Correspondence to: Henri G. Colt, MD, University of California Irvine, Pulmonary/Critical Care Medicine Building 53, Room 119, 101 City Dr South, Orange, CA 92868; e-mail: [hcolt@uci.edu](mailto:hcolt@uci.edu)

DOI: 10.1378/chest.130.5.1605

The IRB is therefore responsible for assuring the following: (1) the risks to research subjects are minimized and are reasonable in relation to anticipated benefits; (2) the welfare and human rights of subjects are protected and informed consent is sought from each prospective subject or the subject's legally authorized representative; (3) such informed consent is appropriately documented; (4) adequate provisions for monitoring data collection are in place to assure the safety, and physical, emotional, and mental well-being of research subjects; (5) the confidentiality of data and the privacy of subjects are assured; and (6) researchers are qualified to conduct the described research on human subjects. In carrying out its obligations, an IRB may approve, disapprove, or require modifications to research protocols. It may also suspend or terminate its approval of ongoing or previously approved research.<sup>2</sup> Each IRB also follows precise policies and procedures in order to identify research proposals that are exempt from regulation. These may or may not be identical to federal and state regulations. In addition, many IRBs in the United States have been seeking voluntary accreditation by the Association for the Accreditation of Human Research Protection Programs, which is an action that assures the quality and standardization of the IRB review and approval process.

In the writing of a research proposal, it is essential to recognize that IRB review will be necessary before the research can commence. Most institutions also require research studies to undergo IRB review, even in cases in which research might be judged to be exempt from the federal regulations. In these cases, a formal letter stating that the research study is IRB-exempt is usually necessary to satisfy oversight requirements for the funding agency. IRB approval can take anywhere from weeks to months, depending on how often the IRB committee meets, workload, staffing, and the types and complexities of the research being evaluated. Having one's IRB application perfectly written according to accepted guidelines, therefore, makes the work of the IRB easier, expedites the review process, and helps to ensure that research is being conducted professionally and according to ethical standards.

#### EXPLICATION

A complete IRB application submission is one that addresses the research justification and plan in sufficient detail, and thereby provides the IRB reviewers with adequate information to make a risk-benefit assessment on the research, as well as a final determination of the approvability of the project. Indeed, a lack of specificity and gaps in the information supplied via the

IRB submission process will only prompt the IRB to pose a multitude of questions to the investigator until the picture of the research proposal is complete enough to make the necessary determinations.

In this regard, most IRBs will require that the complete IRB submission contain the following: (1) an institution-specific application for new and continuing research protocols; (2) a protocol narrative that describes the purpose, hypotheses, and procedures for the research, but also addresses risk and benefit, alternative options, disclosure of the investigator's financial interest, authorization for the release of information (including the creation, use, or disclosure of protected health information that requires additional protections under the Health Information Portability and Accountability Act, also known as HIPAA), research recruitment plan and advertisements, the consenting process, and the reporting of adverse events; and (3) consent forms that are appropriate to the research complexity and the needs of the population being studied. In California, all human subjects must also be given a copy of the Experimental Subject's Bill of Rights.

Indeed, a major responsibility of the IRB is to assure that informed consent documents are written in such a way that all potential research subjects are able to understand the risks and benefits of the proposed research. As stated in Title 45, Part 46, of the Department of Health and Human Services Protection of Human Subjects policy (often called "The Common Rule" because these regulations have been jointly adopted by 14 federal agencies as a common framework to guide the protection of human research subjects): "The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent whether oral or written may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence."<sup>3</sup>

IRB applications are fraught with common mistakes that can be quickly and easily rectified with appropriate attention to detail and consistency in the documents. The clinician investigators who are submitting IRB applications, while certainly viewed as experts in their particular field, must remember that the research rationale and scientific background must be understandable to the sophisticated IRB reviewer but must also be understandable to the lay nonscientific reviewer, who is a federally mandated member of all constituted IRB committees. Therefore, one should make no assumptions about the knowledge base of the potential committee member

reviewers and should provide sufficiently simplistic but broad knowledge that justifies the conduct and/or continuation of the research proposal. Examples of commonly omitted details include the volume of peripheral blood being drawn, the length of subject visits, the lack of a prorated compensation plan for partially completed research procedures, and the lack of quantifying radiograph exposure in imaging studies. The investigator must remember that the primary charge of the IRB is to protect the humans who are the subjects of research. Details are important to enable IRB reviewers to make the determination of overall risk.

Consistency across all documents is another common problem in the application submission process. This means that the application, protocol narrative, consent, and sponsor-generated documents must all contain and provide consistently detailed information. Another common pitfall concerns the provision of "lay" language in the informed consent document, which should be written at no higher than a sixth to eighth grade reading level for an adult participant. This becomes especially challenging in complex biomedical research protocols, and may require many more words, and ultimately a longer consent, in order to achieve this level of understanding. Word-processing programs such as Microsoft Word are helpful in this regard because they provide a readability score after the program finishes checking spelling and grammar (see Tools-spelling and grammar-options-readability statistics).

Additionally, when the type of research (*eg*, drugs, devices, food, and biological agents) falls under the umbrella of the FDA, other aspects of the research application may become problematic. For example, the IRB will need information on the Investigational New Drug application or the Investigational Device Exemption number and filing date. Does a private sponsor hold these applications with the FDA or is this research investigator-initiated? Unlike research regulated by the Department of Health and Human Services, for research regulated by the FDA the informed consent document must specifically provide access to the participant's research records for this agency.

### TAKE-HOME LESSON

Contrary to many researchers' beliefs, the IRB is not a roadblock to successful research. Rather, an effective IRB should be viewed as an asset to an institution, keeping the institution out of trouble because it assures that researchers are compliant with federal and state regulations. Because attention to detail, consistency, and sensitivity to research risks

are of paramount importance, an IRB is effective by helping the researcher identify and institute ways to manage those risks. There is no reason, therefore, for investigators to downplay patient risk so that the research proposed appears safer than it actually is.

The IRB helps researchers by looking for risks in a research proposal that the investigator may have overlooked or underemphasized, thereby protecting the researcher, the institution, and all potential research subjects. The IRB chair is influenced by the burden inherent in serving as an institutional official charged with the enforcement of federal and state regulations, along with local policy and interpretation of regulation. The IRB chair frequently also wears an investigator hat, thereby living under the same regulatory infrastructure for one's own research agenda.

Investigators should recall that every IRB must have at least one nonscientific lay member from the community. Protocols, therefore, including the background information necessary to justify the research project, should be written clearly using nontechnical language. Information from background articles and references should be summarized in an easily understandable fashion, because an IRB should not approve a protocol that its members cannot easily comprehend.

### CONCLUSION

The formula for success through the IRB review and approval processes can be summarized as follows: simplify, use simplified language that is easy to understand; justify, provide rationale for the study, the design, the risk to subjects; protect, make clear the many ways that the protection of subjects is provided throughout the research experience; complete, provide complete detailed information in all areas of the required documents; and be consistent, achieve consistency of the information provided in each section and across study-related documents. In this way, investigators writing for an IRB are sure to explain in simple terms the reason for the research and its risks to human subjects, and to clearly demonstrate how those subjects will be protected from risk.

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This information is current as of March 26, 2009

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