

## Ethical Framework for Clinical Research

**Summary:** To develop a comprehensive framework of ethical guidance for the design, conduct, and review of clinical research; to apply this framework to various cases, and to examine certain controversial ethical issues relating to clinical research in light of the framework.

**Section:** Human Subjects Research- Unit on Clinical Research

**Principal Investigator:** Christine Grady RN Ph.D.

**Collaborators:** Bioethics  
Donna Chen MD  
Ezekiel J. Emanuel MD Ph.D.  
Heidi Forster JD  
Frank Miller PhD  
Jonathan Rackoff BA  
David Wendler PhD

NIH:  
Greg Folkers MPH, NIAID  
Anthony Fauci MD, NIAID  
Jack Killen MD, NIAID  
Donald Rosenstein MD, NIMH

Non- NIH  
John Arras PhD, University of Virginia  
Robert Crouch, PhD, University of Virginia  
Jonathan Moreno PhD, University of Virginia  
Andrew Shorr MD, MPH, Walter Reed Army Medical Center

**Background:** Although clinical research has resulted in significant benefits for society, it continues to pose profound ethical questions. Ethical questions in clinical research have been at the forefront of bioethics from its emergence as a field of inquiry in the mid 1960s to the present. A literature has developed on ethical principles and guidelines governing clinical research and their application to particular studies; however, ethical reflection on clinical research, on the whole, has manifested important theoretical and practical limitations. One result has been the development of competing guidelines, often without accessible justification for what the guidelines require. Another consequence has been

confusion about interpretation and application of the various guidelines and regulations.

First, although several ethical requirements appear necessary to make clinical research ethical, the existing guidance and literature have overemphasized informed consent as the key ethical requirement. In fact, informed consent is not sufficient to make clinical research ethical; nor is it necessary in all clinical investigation. Spurred by available guidance, investigators, IRBs, regulators and others tend to focus on informed consent at the expense of other critical aspects of ethical research. In addition, concerns about compliance and risk aversion have encouraged thinking of informed consent as primarily the signing of a long and legalistic document. Because achieving truly voluntary and informed consent in practice can be challenging, further work on the elements of informed consent and how much moral weight they hold in research is critical.

Second, ethical norms and principles pertinent to the care of patients have been uncritically applied to clinical research without appreciating the ethically significant differences between the pursuit of generalizable knowledge characteristic of clinical investigation and the personalized therapeutic attention characteristic of patient care. The blurring of these two activities has led to some confusion on the part of investigators and reviewers in determining the appropriate scope of their responsibilities, as well as to misunderstanding on the part of research participants. Bioethicists have also tended to conflate these two domains.

Third, ethical guidance has been promulgated without sufficient attention to the methodologies of clinical research and the practical contexts and complexities in which studies are conducted. The application and specification of ethical guidance to various types of studies and research contexts requires careful deliberation and nuanced analysis.

**Objectives:**

- (1) To develop a comprehensive and consistent framework delineating and explicating the ethical requirements appropriate for clinical research;
- (2) To apply this ethical framework to various domains or aspects of clinical investigation;
- (3) To undertake ethical analyses of controversial issues relating to the design and conduct of clinical research;
- (4) To undertake focused empirical research aimed at elucidating ethical issues relevant to the conduct or regulation of clinical research.

**Methodology:** Members of the Department reviewed available literature on the ethics of clinical research, including the existing guidelines and codes of research ethics. These included: the Nuremberg Code, The Declaration of Helsinki (all revisions), the Belmont Report, the US Common Rule and other parts of 45 CFR46, the FDA regulations, the International Conference on Harmonization Guidelines for Good Clinical Practice (ICH/GCP), the Council of International Organizations of Medical Sciences (CIOMS) guidelines, and various national guidelines governing human subjects' research. Claims, principles, and arguments in the articles and guidance were analyzed and discussed among members of the Department in various settings, informally, at research team meetings, and at works-in-progress meetings.

We attempted to synthesize and clarify existing guidance by proposing a systematic framework for evaluating the ethics of clinical research studies. Members of the department are regularly presented with an assortment of ethical issues confronting clinical researchers through participation in various intramural NIH IRBs, membership on an assortment of Data and Safety Monitoring Committees, participation in the Bioethics Consultation Service and on clinical rounds, as well as through different educational activities. These activities also provide an opportunity to test the extent to which our framework is helpful in elucidating difficult ethical challenges in clinical research.

The framework has been applied to specific examples that have posed either timely or extraordinary challenges to the research community.

**Results:**

Drawing on philosophies underlying the major codes, declarations, and literature relevant to human subjects' research, we proposed a systematic framework of 7 requirements for ethical clinical research. The seven requirements are:

- Value-the research should answer a question that will enhance health or provide useful knowledge addressing health;
- Validity- the research should have an appropriate, rigorous, and feasible design and methodology;
- Fair subject selection- subjects should be selected based on scientific appropriateness and evaluation of risk;
- Favorable risk-benefit ratio—risks should be minimized and justified by the benefits, if any, to the participants and the anticipated value of the knowledge to be gained. Benefits to subjects should be maximized.
- Independent review- there should be prospective and periodic ethical assessment of research protocols by independent committees or designees;
- Informed consent- there should be adequate processes for providing information and promoting the voluntary enrollment of subjects; and
- Respect for Enrolled Subjects—subjects' rights and welfare should be respected and protected throughout and at the conclusion of the study.

We argued that these requirements provide a framework that is coherent and systematic for use by investigators and review bodies, although we recognize that reasonable disagreement might arise about the interpretation of the requirements and the application of requirements to specific studies.

Using the requirements proposed in this framework, members of the department have applied the framework to particular kinds of research or particular studies, including infectious challenge studies, vaccine studies, autism research, research involving healthy volunteers, and a case study of an industry sponsored clinical trial. The framework has also been applied and further specified through the development of benchmarks for international research (see write up on Multinational research), and through consideration of HIV research in the international context.

In collaboration with colleagues from the University of Virginia, we have also assembled an anthology of seminal articles in the literature on the ethics of clinical research. The proposed ethical framework was used to organize the existing literature for this textbook. Members of the department as co-editors wrote introductions to the various sections of the text. This text is scheduled to be published by Johns Hopkins University Press in 2003.

As requested by the President's Council on Bioethics, we analyzed and described the current problems facing the human research oversight system, examined current proposals for reform and proposed a solution. The solution calls for restructuring the system, moving away from local IRBs to regional review boards which would have responsibility not only for oversight of research, but also for educating investigators and deliberating and developing policy on certain aspects of research.

In addition, members of the department have worked to further elucidate the implementation of specific requirements, such as informed consent, independent review, and value.

### **Future Directions:**

Members of the department are in the process of developing a multi-authored textbook on the ethics of human subjects' research that is based on the 7 requirements framework. The book will incorporate the bioethics scholarship of leading experts around the world with the aim of providing comprehensive ethical guidance about the ethics of clinical research for bioethicists, investigators, IRB members, and students. A detailed outline of the textbook has been prepared, encompassing 12 sections and 74 chapters. Each of the 12 sections will be edited by one of 5 editors from the Department, who will also prepare an introduction to the issues covered in that section. The editors collectively will write an introduction to the text as a whole. As currently planned, 16 of the chapters will be authored, or co-authored, by members of the Department, offering an opportunity to consolidate and expand research undertaken over the

past several years. Several outside authors have committed to contributing a chapter and Oxford University Press, having reviewed the proposal, has expressed a strong interest in the project. Work on writing the chapters will begin in early 2003, the manuscript will be delivered to the publisher by January 2004, and the first edition will be in print by the end of 2004. If the textbook is successful, consideration will be given to revising it periodically with the goal of continuing to offer a valuable resource.

Members of the department will also continue to apply the framework to particular cases and to further elucidate particular aspects of the different requirements in the framework.

### **Publications:**

Grady C. Thinking further about value: commentary on "A Taxonomy of Value in Clinical Research" *IRB: Ethics and Human Research* 2002;

Wendler D, Miller F. Deception in the Pursuit of Science. Submitted to *Annals of Internal Medicine*

Chen D, Miller F, Rosenstein D. Ethical Aspects of Research into the Etiology of Autism.

Killen J, Grady C, Folkers G, Fauci A. Ethics of clinical research in the developing world *Nature Reviews/Immunology* 2002; 2: 210-215

Wendler D, Rackoff J. Consent for Continuing Research Participation: what is it and when should it be obtained? *IRB: Ethics and Human Research*.2002; 24:1-6.

Miller F, Shorr A. Ethical Assessment of Industry-Sponsored Clinical Trials: A Case Analysis. *Chest* 2002; 121: 1337-1342

Grady C. Ethical Principles in Clinical Research. Chapter 2 in J. Gallin (Ed) Principles and Practice of Clinical Research. New York: Academic Press. 2002 Pages: 15-26

Forster H, Emanuel E, and Grady C. The 2000 Revision of the Declaration of Helsinki: A Step Forward or More Confusion? *Lancet* 2001; 358:1449-53

Wendler D, Rackoff J. Respecting individual autonomy: what's a signature got to do with it? *IRB: Ethics and Human Research* 2001; 23:1-4.

Grady, C. Clinical Research: The Power of the Nurse. *AJN Viewpoint* 2001; 101(9):11

Miller F and Grady C. The Ethical Challenge of Infection-Inducing Challenge Studies, *Clinical Infectious Diseases*\_2001; 33: 1028-1033.

Emanuel E, Wendler D, Grady C. What makes clinical research ethical? *Journal of the American Medical Association* 2000; 283(20):2701-11