Ethical and Regulatory Aspects of Clinical Research
NIH CC Department of Bioethics
Wednesdays, September 25 - November 13, 2019

There is no fee for this course, but a textbook, **The Ethical and Regulatory Aspects of Clinical Research (JHU Press)** is required. The book is available in the FAES Bookstore in Building 10 and also can be ordered from commercial bookstores and websites.

September 25, 2019 **Session 1: Ethical Framework, Bench to Bedside, and IRB Function/Purpose**

8:30 - 8:40 **Introduction**

8:40 - 9:20 **Framework for the Ethics of Research with Human Subjects**
Christine Grady RN PhD
Chief, NIH Clinical Center Department of Bioethics

9:20 - 9:30 **Discussion**

Readings (textbook):
Chapter 5. "The Nuremberg Code."
Chapter 6. "The Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects."
Chapter 7. "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research."

Readings:
Emanuel E., Wendler D., & Grady C. "What Makes Clinical Research Ethical?" *JAMA* 2000; 283 (20): 2701-2711

9:30 - 9:45 **Break**

9:45 - 10:30 **History, Scandals and Tragedies: Beecher, Tuskegee, Willowbrook and the Rest**
Susan E. Lederer PhD
Robert Turell Professor and Chair, Medical History and Bioethics
University of Wisconsin

10:30 - 10:40 **Discussion**

Readings (textbook):
Chapter 1. US Medical Researchers and Nuremberg
Chapter 2. Katz, J., et al. "The Jewish Chronic Disease Hospital Case."
Chapter 3. Beecher, H.K. "Ethics and Clinical Research."

Chapter 4. Brandt, A.M. "Racism and Research: The Case of the Tuskegee Syphilis Study."

Jones D.S., Grady C., & Lederer S. "Ethics and Clinical Research" — The 50th Anniversary of Beecher's Bombshell**.** *N Engl J Med* 2016. 374(24): 2393-2398.

10:40 - 11:20 **Bench to Bedside or Bedside to Bench: The Ethics of the Investigator-Participant Relationship**
Steve Joffe MD MPH
Chief, Division of Medical Ethics
Emanuel and Robert Hart Professor of Medical Ethics and Health Policy
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine

11:20 - 11:30 **Discussion**

Readings (textbook):
Chapter 13. Hellman S. and Hellman D. "Of Mice But Not Men: Problems of the Randomized Clinical Trial."

Readings:
Joffe S., & Miller F. "Bench to Bedside: Mapping the Moral Terrain of Clinical Research." *Hastings Center Report*, March April 2008

Miller F., & Rosenstein D. The Therapeutic Orientation to Clinical Trials. *NEJM* 1993

October 2, 2019 **Session 2: IRBs, Risks and Benefits, and the Ethics of Research with Children**

8:30 - 9:15 **Purpose and Function of IRBs: Successes and Current Challenges**
Sara Hull PhD
Director, NHGRI Bioethics Core
Faculty, NIH CC Department of Bioethics

9:15 - 9:25 **Discussion**

Readings (textbook):
Chapter 85. Edgar H. and Rothman D. "The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation."

Readings:

The Common Rule, at https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML

King, NMP Who's Winning the IRB Wars? The Struggle for the Soul of Human Research. *Perspectives in Biology and Medicine*, Volume 61, Number 3, Summer 2018, pp. 450-464. https://muse.jhu.edu/article/704386/pdf

Grady C. Institutional Review Boards: Purpose and Challenges. *Chest*. 2015 Nov 1; 148(5):1148-55. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4631034/

9:25 - 10:10 **Risks and Benefits**
Dave Wendler PhD
Head of Section on Ethics and Research
NIH Clinical Center Department of Bioethics

10:10 - 10:20 **Discussion**

10:20 - 10:35 **Break**

Readings (textbook):
Chapter 42. Freedman B., Fuks A., and Weijer C. "*In loco parentis*: Minimal Risk as an Ethical Threshold for Research upon Children."

Readings:
King, N. Defining and Describing Benefit Appropriately in Clinical Trials
J Law Med Ethics 2000; 28:332-43

Rid, A.; Emanue,l E.; Wendler D. Evaluating the Risks of Clinical Research.
JAMA. 2010; 304(13):1472-1479

Weijer, C. & Miller, P.B. When Are Research Risks Reasonable in Relation to Anticipated Benefits? *Nature Medicine* 2004; 10(6):570-3

10:35 - 11:20 **Ethics of Research with Pregnant Women**
Maggie Little PhD
Senior Research Scholar, Professor of Philosophy, Director of Ethics Lab
Georgetown University

11:20 - 11:30 **Discussion**

Readings (book)
Chapter 24. Dresser, R. Wanted: Single, White Male for Medical Research
Chapter 25. Weijer, C and Crouch R. Why Should We Include Women and Minorities in Randomized Controlled Trials.

Readings (CD):
Little M, Lyerly A, Faden R. Pregnant women and medical research: a moral imperative. *Bioethics Forum* 2009; 2(2): 60-65

OCTOBER 9, 2019 - NO CLASS YOM KIPPUR

October 16, 2019 **Session 3: Ethics of Pragmatic Trials, Ethics of Randomized Clinical Trials, and Ethics of Vaccine Research**

8:30 - 9:15 **Ethics of Pragmatic Trials**
Scott Kim MD PhD
Senior Investigator
NIH Clinical Center Department of Bioethics

9:15 - 9:25 **Discussion**

Readings:
Kim S. Y. H. Ethical issues in pragmatic trials of "standard-of-care" interventions in learning health care systems. *Learn Health Sys*. 2017:1-5.

Platt, R., Kass, N. E., & McGraw, D. (2014). Ethics, Regulation, and Comparative Effectiveness Research: Time for a Change. *JAMA*, 311(15), 1497-1498. doi: 10.1001/jama.2014.2144

Kim, S. Y. H., & Miller, F. G. (2015). Varieties of Standard-of-Care Treatment Randomized Trials: Ethical Implications. *JAMA*, 313(9), 895-896. doi: 10.1001/jama.2014.18528

9:25 - 9:40 **Break**

9:40 - 10:25 **Ethics of Randomized Clinical Trials: Clinical Equipoise**
Robert Truog MD
Director, Harvard Center for Bioethics
Frances Glessner Lee Professor of Legal Medicine,
Professor of Anaesthesia (Pediatrics)
Harvard Medical School

10:25 - 10:35 **Discussion**

Readings (textbook):
Chapter 11. Levine R. "Research and Practice."
Chapter 13. Hellman S. and Hellman DS. "Of Mice but Not Men: Problems of the Randomized Clinical Trial."
Chapter 14. Freedman B. "Equipoise and the Ethics of Clinical Research"
Chapter 15. Truog R. "Randomized Controlled Trials: Lessons from ECMO"

10:35 - 11:20 **Ethics of Vaccine Research**
Holly Taylor PhD MPH
NIH Clinical Center Department of Bioethics

11:20 - 11:30 **Discussion**

Readings:
Dawson L. and Zwerski S. Clinical Trial Design for HIV Prevention Research: Determining Standards of Prevention. *Bioethics*. 2015 Jun; 29(5): 316–323.

Bambery B., Selgelid M., Weijer C., Savulescu J., & Pollard A. Ethical Criteria for Human Challenge Studies in Infectious Diseases. *Public Health Ethics*. 2016; 9 (1): 92–103

October 23, 2019 **Session 4: Fair Subject Selection, Recruitment and Retention, and Participant Panel**

8:30 - 9:15 **Fair Subject Selection**
Holly Taylor PhD MPH
NIH Clinical Center Department of Bioethics

Readings (textbook):
Chapter 4. Brandt, A.M. "Racism and Research: The Case of the Tuskegee Syphilis Study."(assigned for Session 1)
Chapter 22. Jonas, H. "Philosophical Reflections on Experimenting with Human Subjects."
Chapter 24. Dresser, R. "Wanted: Single, White Male for Medical Research."
Chapter 25. Weijer, C. and Crouch, R.A. "Why Should We Include Women and Minorities in Randomized Controlled Trials?"

9:15 - 9:25 **Discussion**

9:25 - 10:10 **Recruitment and Retention**
Dave Wendler PhD
NIH Clinical Center Department of Bioethics

10:10 - 10:20 **Discussion**

Readings (textbook):
Chapter 27. Dickert, N. and Grady, C. "What's the Price of a Research Subject? Approaches to Payment for Research Participation."
Chapter 29. McNeil, P. "Paying People to Participate: Why Not?"
Chapter 73. Lind, S.E. "Finder's Fees for Research Subjects."

10:20 - 10:35 **Break**

10:35 - 11:30 **Participant Panel**

October 30, 2019 **Session 5: Informed Consent, Research with Those with Impaired Capacity for Consent, and Research Ethics Consultation**

8:30 - 9:15 **Informed Consent**
Christine Grady RN PhD
NIH Clinical Center Department of Bioethics

9:15 - 9:25 **Discussion**

Readings (textbook):
Chapter 30. Levine, R.J. "Consent Issues in Human Research."
Chapter 31. Ingelfinger, F.J. "Informed (But Uneducated) Consent."
Chapter 32. Freedman, B. "A Moral Theory of Informed Consent."
Chapter 33. Truog R., et al. «Is Informed Consent Always Necessary for Randomized, Controlled Trials?"

Readings:
Grady C. Enduring and Emerging Challenges of Informed Consent, *New Eng J Med*, 2015;372 (9):855-62.

9:25 - 10:10 **Research Involving Persons at Risk for Impaired Decision-Making**
Scott Kim MD PhD
Senior Investigator
Department of Bioethics, NIH Clinical Center

10:10 - 10:20 **Discussion**

Readings (textbook):
Chapter 38. National Bioethics Advisory Commission. Excerpts from "Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity."

Readings:
NIH SOP 14E: Research Involving Adults Who Are or May Be Unable to Consent Available at https://ohsr.od.nih.gov/public/SOP_14E_v2_05-26-16.pdf

Kim S.Y., Appelbaum P., Jeste D., & Olin J. Proxy and Surrogate Consent in Geriatric Neuropsychiatric Research: Update and Recommendations. *Am J Psychiatry* 2004; 161:797806

Kim S.Y. The ethics of informed consent in Alzheimer disease research. Nat Rev Neurol. 2011 May 24; 7(7): 410–414.

10:20 - 10:35 **Break**

10:35 - 11:20 **Research Ethics Consultation**
Marion Danis MD

Readings:
Beskow L.M., Grady C., Iltis A.S, Sadler J.Z., Wilfond B.S. Points to Consider: The Research Ethics Consultation Service and the IRB *IRB* 31, no. 6(2009):1-9.

Porter K.M., Danis M., Taylor H., Cho M., Wilfond B.S. on behalf of the Clinical Research Ethics Consultation Collaborative Repository Group. The Emergence of Clinical Research Ethics Consultation: Insights from a National Collaborative. *Am J Bioeth* 18 no. 1(2018): 39-45.

November 6, 2019 **Session 6: Ethical Issues in International Research**

8:30 - 9:15 **Ethical Issues in International Research: Introduction and Standard of Care**
Annette Rid MD, PhD
NIH Clinical Center Department of Bioethics and Georgetown University

9:15 - 9:25 **Discussion**

9:25 - 10:10 **Ethical issues in International Research: Post trial obligations**
Joseph Millum PhD
NIH Clinical Center Department of Bioethics and Fogarty International Center

10:10 - 10:20 **Discussion**

Readings:

Emanuel E, Wendler D, Killen J, Grady C. "What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research." *J Inf Dis* 2004; 189:930

Wertheimer A. Exploitation. Chapter 20 in E. Emanuel et al (eds). The Oxford Textbook of Clinical Research Ethics. New York: Oxford University Press, 2008, pages 201-210

Declaration of Helsinki, https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Optional readings:

Standard of Care

CIOMS guideline 5; <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>

Lurie P. and Wolfe S.M. "Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries." *N Engl J Med* 337.12 (1997): 853-6.

Lie R.K., et al. "The standard of care debate: the Declaration of Helsinki versus the international consensus opinion." *Journal of Medical Ethics* 30.2 (2004): 190-193.

Schüklenk U. "The standard of care debate: against the myth of an "international consensus opinion"." *Journal of medical ethics* 30.2 (2004): 194-197.

Post-trial Obligations / Ancillary Care

CIOMS guideline 6
https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

Grady C. "The Challenge of Assuring Continued Post-Trial Access to Beneficial Treatment." *Yale J. Health Policy L. & Ethics* 5 (2005): 425.

Millum J. "Post-Trial Access to Antiretrovirals: Who Owes What to Whom?" *Bioethics* 25.3 (2011): 145-154.

Participants in the 2006 Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries. "The ancillary-care obligations of medical researchers working in developing countries." *PLoS medicine* 5.5 (2008): e90.

Responsiveness & Reasonable Availability

CIOMS guideline 2
https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

Wolitz R., Emanue E., and Shah S. "Rethinking the responsiveness requirement for international research." *The Lancet* 374.9692 (2009): 847-849.

10:20 - 10:35 **Break**

10:35 - 11:30 **Mock IRB- Ebola Treatment Trial**
Annette Rid, MD, PhD

November 13, 2019 **Session 7: Ethics of Genetics Research and Incidental Findings, and Ethical Issues in *All of Us***

8:30 - 9:15 **Ethics of Genetics Research and Incidental Findings**
Leila Jamal PhD
NIAID, and NIH Clinical Center Dept of Bioethics

9:15 - 9:25 **Discussion**

9:25 - 10:10 **Ethics of Genetics Research and Incidental Findings**
Ben Berkman JD MPH
NHGRI Bioethics Core and NIH Clinical Center Dept of Bioethics

10:10 - 10:20 **Discussion**

Readings:
President's Commission for the Study of Bioethical Issues. Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts. 2013. Executive Summary, pages 1-20, available at https://bioethicsarchive.georgetown.edu/pcsbi/node/3183.html

10:20 - 10:35 **Break**

10:35 - 11:20 **Ethical Issues in the *All of Us* Research Program**
Katherine Blizinsky, Ph.D
Policy Director, *All of Us* Research Program
NIH

11:20 - 11:30 **Discussion**

Readings:
Collins F, Varmus H. (2015). A New Initiative on Precision Medicine. *NEJM*. 372 (9): 793-795.

Sankar PL, Parker LS. The Precision Medicine Initiative's All of Us Research Program: an agenda for research on its ethical, legal, and social issues. *Genet Med*. 2017 Jul;19(7):743-750.

Rivera SM, et al. Modernizing Research Regulations Is Not Enough: It's Time to Think Outside the Regulatory Box. *Am J Bioeth*. 2017 Jul;17(7):1-3.

Kraft SA, et al. Beyond Consent: Building Trusting Relationships With Diverse Populations in Precision Medicine Research. *Am J Bioeth.* 2018 Apr;18(4):3-20.

> *Comment:* Sabatello M, et al. Trust, Precision Medicine Research, and Equitable Participation of Underserved Populations. *Am J Bioeth.* 2018 Apr;18(4):34-36.

Minari J, et al. Tensions in ethics and policy created by National Precision Medicine Programs. *Hum Genomics*. 2018 Apr 17;12(1):22.

Beskow LM, et al. Thought leader perspectives on benefits and harms in precision medicine research. *PLoS One*. 2018 Nov 26;13(11):e0207842.

Hammack CM, et al. Thought Leader Perspectives on Participant Protections in Precision Medicine Research. *J Law Med Ethics.* 2019 Mar;47(1):134-148.

Lee SS, et al. Ethics of inclusion: Cultivate trust in precision medicine. *Science*. 2019 Jun 7;364(6444):941-942.

All of Us Research Program Investigators, et al. The "All of Us" Research Program. *N Engl J Med.* 2019 Aug 15; 381(7):668-676.