Ethical and Regulatory Aspects of Clinical Research
NIH CC Department of Bioethics
Wednesdays, Oct 1 to Nov 12, 2014

Course Readings:
Readings are listed under each topic below. The list includes both readings assigned for each session and some additional recommendations.
Assigned readings are found either in the following course textbook (listed by chapter) or on the supplemental course CD provided.

Course Textbook:
Emanuel E, R. Crouch, J. Arras, J. Moreno, and C. Grady. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore: Johns Hopkins University Press 2003. (Available from the FAES bookstore)

October 1, 2014 **Session 1: History, Guidance, and Framework for Ethical Clinical Research**

8:30-8:40 Pre-test and Introduction

8:40-9:30 **Framework for the Ethics of Research with Human Subjects**
Christine Grady RN PhD
NIH Clinical Center Dept of Bioethics

9:30-9:40 **Discussion**

Readings: (book)
Chapter 5. The Nuremberg Code
Chapter 6. The Declaration of Helsinki
Chapter 7. The Belmont Report

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

9:40-10:00 **Break**

10:00-10:50 **History, Scandals and Tragedies: Beecher, Tuskegee, Willowbrook and the Rest**
Susan E. Lederer PhD
Robert Turell Professor of Medical History and Bioethics, Chair
University of Wisconsin

10:50- 11:00 **Discussion**

Readings: (book)
Chapter 1. Faden et al. "US medical researchers, the Nuremberg Doctors Trial, and the Nuremberg Code."
Chapter 2. Katz et al. "The Jewish chronic disease case,"
Chapter 3. Beecher, H. "Ethics and clinical research."
Chapter 4. Brandt, A. "Racism and Research: The case of the Tuskegee Syphilis Study.".

Readings: (CD)
Rothman D, Beecher H. Ethics and Human Experimentation. *NEJM* Nov 5, 1987; 317 (19):1195-1199.

11:00- 11:30 **The DHHS Secretary's Advisory Committee for Human Research Protections**
Jeffrey R. Botkin, MD, MPH
Chair, SACHRP
Professor of Pediatrics and Medical Ethics
Associate Vice President for Research
University of Utah

October 8, 2014 Session 2: IRB review, Randomized Clinical Trials, and Research with Children

8:30-9:15 **Purpose and Function of IRBs: Successes and Current Challenges**
Richard Cannon MD
Chair, NHLBI IRB

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

Chapter 8. The Common Rule
Chapter 85. Edgar H, Rothman D. "The Institutional Review Board and Beyond: Future challenges to the ethics of human experimentation."

Readings: (CD)
Emanuel E, et al. Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals. *Annals of Internal Medicine* 2004; 141(4):282-291

Grady C. Do IRBs Protect Human Research Participants? *J Am Med Assoc* 2010; 304(10):1122-1123

Emanuel E, Menikoff J. Reforming the Regulations Governing Research with Human Subjects *NEJM* ; 2011 Jul 25

9:25-10:10 **Ethics of Randomized Clinical Trials: Clinical Equipoise**
Robert Truog MD

Professor of Medical Ethics & Anaesthesia (Pediatrics)
Harvard Medical School

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

Readings: (book)
Chapter 11. Levine R. "Research and practice,"
Chapter 13. Hellman S, & 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

10:20-10:45 **Break**

10:45-11:20 **Research with Children**
Sara Goldkind MD
Research & Clinical Bioethics Consultant

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

Readings: (book)
Chapter 42. Freedman B, Fuks A, Weijer C. "*In loco parentis*: Minimal risk as an ethical threshold for research upon children,"
Chapter 41. Tauer C. "The NIH trials of growth hormone for short stature."
Chapter 43. Leikin S. "Minors assent, consent, or dissent to medical research."

October 15, 2014 **Session 3: Fair Subject Selection**

8:30- 9:10 **Fair Subject Selection**
Dave Wendler PhD
NIH Clinical Center Department of Bioethics

9:10-9:20 **Discussion**

Readings: (CD)
Wendler D. When should 'riskier' subjects be excluded from research? *Kennedy Institute of Ethics Journal* 1998; 8:307-327.
Lyerly AD, Little M, Faden R. Reframing the Framework: Toward Responsible Inclusion of Pregnant Women as Participants in Research. *American Journal of Bioethics* 2011, 11(5):50-1.
Rid A, Emanuel EJ. Ethical considerations of experimental interventions in the Ebola outbreak. Published Online August 21, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61315-5

9:20- 10:05 **Coercion and Undue Inducement**
Alan Wertheimer PhD
NIH Clinical Center Department of Bioethics

10:05-10:15 **Discussion**

Readings: (book)
Chapter 27, Dickert N, Grady C. "What's the price of a research subject"?

Readings: (CD)
Largent E, Grady C, Miller F, Wertheimer A. Misconceptions about coercion and undue influence: reflections on the views of IRB members. *Bioethics*. 2012 Apr 12. doi: 10.1111/j.1467-8519.2012.01972.x. [Epub ahead of print
Emanuel, EJ. Undue Inducement – Nonsense on Stilts. American Journal of Bioethics 2005;5(5):9-13.

Supplementary readings
Chapter 28, Lemmens T, Elliott C. "Justice for the professional guinea pig"
Chapter 29, McNeill P. "Paying people to participate: why not?"

10:15-10:30 Break

10:30-11:30 **MOCK IRB**

Readings: (CD)
Protocol and consent forms

<u>October 22, 2014</u> **Session 4: Risks and Benefits, Research involving persons at risk for impaired decision making**

8:30-9:15 **Risks and Benefits**
Dave Wendler, PhD
NIH Clinical Center Department of Bioethics

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

Readings: (book)
Chapter 42. Freedman B, Fuks A, Weijer C. "*In loco parentis*: Minimal risk as an ethical threshold for research upon children.

Readings: (CD)
King N, Defining and Describing Benefit Appropriately in Clinical Trials
J Law Med Ethics 2000; 28:332-43
Rid A; Emanuel E; Wendler D Evaluating the Risks of Clinical Research.
JAMA. 2010; 304(13):1472-1479

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

Supplemental: Rid A, Wendler D. A Framework for Risk-Benefit Evaluations in Biomedical Research, *Kennedy Institute of Ethics Journal 2011;* Vol. 21, No. 2, 141–179

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

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

Readings: (book)
Chapter 38. National Bioethics Advisory Commission, excerpts from "Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity"

Readings: (CD)
Kim S, Appelbaum P, Jeste D, Olin J. Proxy and Surrogate Consent in Geriatric Neuropsychiatric Research: Update and Recommendations. *Am J Psychiatry 2004; 161:797–806*

Supplementary readings
Kim SY The ethics of informed consent in Alzheimer disease research. *Nat. Rev. Neurol*. advance online publication 24 May 2011

10:20- 10:30 **Break**

10:30- 11:30 **Participant panel**

October 29, 2014 **Session 5: Informed Consent, Comparative Effectiveness Trials, and Conflicts of Interest**

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

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

Readings
Chapter 31 Inglefinger, F. 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?

Supplementary readings not on CD

Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review, *JAMA*. 2004 Oct 6; 292(13):1593-601.

Mandava A, Pace C, Campbell B, Emanuel E, Grady C. The quality of informed consent: mapping the landscape. A review of empirical data from developing and developed countries, *J Med Ethics* 2012; 38:356-365

9:25- 10:10 **Comparative Effectiveness Trials and Informed Consent**
Frank Miller PhD
NIH CC Department of Bioethics

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

Readings CD

Faden R et al. Ethics and Informed Consent for Comparative Effectiveness Research With Prospective Electronic Clinical Data (*Med Care* 2013;51: S53–S57)

Kim S and Miller F. Informed Consent for Pragmatic Trials — The IntegratedConsent Model *N ENGL J MED* 370;8: 769-772

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

10:35- 11:20 **Conflicts of Interest**
Steve Joffe MD MPH
Associate Professor of Medical Ethics and Health Policy
University of Pennsylvania

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

Readings: (book)

Chapter 72. Thompson D. "Understanding Financial Conflicts of Interest"
Chapter 75. Martin, JB and Kasper, DL. "In whose best interest? Breaching the academic-industrial wall."

Readings (CD)

LOEWENSTEIN G, SAH S, CAIN D, THE UNINTENDED CONSEQUENCES OF CONFLICT OF INTEREST DISCLOSURE. *JAMA*, FEBRUARY 15, 2012—VOL 307, NO. 7 669-70

Zinner D, Bjankovic D, Clarridge B, Blumenthal D, Campbell E. Participation Of Academic Scientists In Relationships With Industry. *Health Aff* (Millwood) 2009;28(6):1814–25
Krumholz HM et al. What have we learnt from Vioxx? *BMJ* 2007; 334:120-123
Licurse A, Barber E, Joffe S, Gross C. The impact of disclosing financial ties in research and clinical care: a systematic review. *Arch Intern Med*. 2010 Apr 26; 170(8):675-82.
Stossel TP. Regulating academic-industrial research relationships--solving problems or stifling progress? *N Engl J Med*. 2005 Sep 8; 353(10):1060-5.

Nov 5, 2014 **Session 6: Ethics of International Research**

8:30-9:15 **Exploitation**
Alan Wertheimer PhD
NIH Clinical Center Department of Bioethics

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

9:25 - 10:10 **Post trial Obligations and reasonable availability**
Seema Shah JD
NIH Clinical Center Department of Bioethics and
NIAID Division of AIDs

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

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

10:35-11:20 **Case discussion**
Joe Millum PhD
NIH Clinical Center Department of Bioethics and Fogarty International Center

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

Readings:
Declaration of Helsinki, http://www.wma.net/en/30publications/10policies/b3/
NIH guidance on ART http://grants.nih.gov/grants/policy/antiretroviral/guidance.doc

Readings: (CD)
Excerpts from CIOMS
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

Supplementary

Chapter 65. Lurie P & Wolfe S. "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries"
Chapter 68. Participants in the 2001 conference on Ethical Aspects of Research in Developing Countries. Fair benefits for Research in Developing countries.

November 12, 2014 **Session 7: Ethics and Genetics Research**

8:30-9:15 **Ethical Issues in the Use of Stored Tissue and Data**
Sara Chandros Hull PhD
NHGRI and NIH Clinical Center Department of Bioethics

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

Ethical Issues in the Use of Stored Tissue and Data

Readings: (CD)
Paltoo D et al. Data use under the NIH GWAS Data Sharing Policy and future directions. Nature Genetics 2014. Vol 46 (9).
Hirutska V et al Views of Biobanking Research Among Alaskan Native People: the Role of Community Context. *Progress in Community Health Partnerships*. 2012. Vol 6.2, pages 131-139.
Hull S. et al. Patients' Views on Identifiability of Samples and Informed Consent for Genetic Research. *AJOB* 8(10): 62–70, 2008

Wendler D (2006) "One-time general consent for research on biological samples," BMJ, 332: 544.

9:25-10:10 **How to think about Incidental Findings**
Ben Berkman JD
NHGRI and NIH Clinical Center Department of Bioethics

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

Readings: (CD)
Ravitsky, Vardit and Wilfond, Benjamin S.(2006) 'Disclosing Individual Genetic Results to Research Participants', *The American Journal of Bioethics*. 2006. 6: 6, 8 — 17,
Feero WG, Guttmacher A, Collins F. Genomic Medicine — An Updated Primer *NEJM* 2010. 362:2001-11
Wolf S et al. Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations 2008. *J Law, Med & Ethics*

F A Miller, R Christensen, M Giacomini, J S Robert. Duty to disclose what? Querying the putative obligation to return research results to participants *J Med Ethics* 2008. 34: 210-213
American College of Medical Genetics and Genomics, ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing, available at: https://www.acmg.net/docs/ACMG_Releases_Highly-Anticipated_Recommendations_on_Incidental_Findings_in_Clinical_Exome_and_Genome_Sequencing.pdf
Catherine Gliwa & Benjamin E. Berkman, Do Researchers Have an Obligation to Actively Look for Genetic Incidental Findings? *The American Journal of Bioethics*, 13:2, 32-42 (2013)

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

10:35- 11:20 **Case**

11:20- 11:30 **Post tests and evaluations**