Ethical and Regulatory Aspects of Clinical Research
NIH CC Department of Bioethics
Wednesdays, September 28-November 16, 2016

Course Readings:
Readings are listed under each topic below. The list includes both readings assigned for each session and some additional recommendations (supplementary- citations only). 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 or Amazon)

September 28, 2016 **Session 1: History and Framework for Ethical Clinical Research**

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

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

9:20-9:30 **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

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

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

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

Readings: (book)
Chapter 3. Beecher, H. "Ethics and clinical research."

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

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

Stark L. The unintended ethics of Henry K. Beecher. *The Lancet* 2016.

Supplementary:
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 4. Brandt, A. "Racism and Research: The case of the Tuskegee Syphilis Study.".

10:40- 11:20 **Changes to the Common Rule**
Ivor Pritchard, OHRP

11:20-11:30 Discussion

Readings:

Notice of Proposed Rulemaking (NPRM) available at
https://www.federalregister.gov/articles/2015/09/08/2015-21756/federal-policy-for-the-protection-of-human-subjects

October 5, 2016 Session 2: IRBs, Fair subject selection, and participant perspectives

8:30-9:110 **Purpose and Function of IRBs: Successes and Current Challenges**
Sara Hull PhD
Chair, NHGRI IRB

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

Readings: Textbook
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

9:20-10:15 **Fair Subject Selection**
Dave Wendler PhD
NIH Clinical Center Department of Bioethics

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

Readings: (CD)
Wendler D. When should 'riskier' subjects be excluded from research? *Kennedy Institute of Ethics Journal* 1998; 8:307-327.

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

Emanuel E, Joffe S, Grady C, Wendler D, Persad G. Clinical research: Should patients pay to play? *Science Translational Medicine* 29 July 2015 Vol 7 Issue 298 298ps16

Meltzer L, Childress J. What is Fair Subject Selection. Chapter 35 from the Emanuel et al Oxford Textbook of Clinical Research Ethics. Oxford U Press, 2008; page 377-85.

10:15-10:30 **Break**

10:30-11:30 **Panel of research perspectives**

October 12- NO CLASS –YOM KIPPUR

October 19, 2016 **Session 3: Risk and Benefits, Research with Children, and Research with Pregnant Women**

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 **Ethics of Research with Children**
Robert "Skip" Nelson MD
Director of Ethics and Deputy Director,
Office of Pediatric Therapeutics
US Food and Drug Administration

10:10-10:20 **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."

Readings (CD):
Roth-Cline M, Gerson J, Bright P,. Lee C, Nelson R. Ethical Considerations in Conducting Pediatric Research. From *Pediatric Clinical Pharmacology*, 2011

10:20-10:35 Break

10:35-11:20 **Ethics of Research with Pregnant women**
Maggie Little PhD
Director of the Kennedy Institute of Ethics, and Associate Professor of Philosophy

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 26, 2016 **Session 4: Informed consent, research with adults with impaired decision making, and the ethics of research with big data**

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

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

Readings (book)
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?

Readings (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

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
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

NIH Policy M87-4 Research involving adults who are or may be unable to consent. Available at http://cc-internal.cc.nih.gov/policies/PDF/M87-4.pdf

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; 161:797806

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

10:20-10:35 Break

10:35-11:20 **Research with Big Data**
Jeff Kahn PhD
Berman Institute of Bioethics, JHU

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

Readings (CD):
Effy Vayena, Marcel Salathé, Lawrence C. Madoff, John S. Brownstein, "Ethical Challenges of Big Data in Public Health," PLOS Computational Biology, February 9, 2015; http://dx.doi.org/10.1371/journal.pcbi.1003904.

Jeffrey P. Kahn, Effy Vayena, Anna C. Mastroianni, "Learning as We Go: Lessons from the Publication of Facebook's Social-computing Research," PNAS 111(38):13677-13679; 2014; doi: 10.1073/pnas.1416405111.

Nov. 2, 2016 **Session 5: Ethics of Randomized Trials, Research with Stored Tissue and Data, and Conflicts of Interest**

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**

Grady C, Eckstein L, Berkman B, Brock D, Cook-Deegan R, Fullerton SM, Greely H, Hansson MG, Hull S, Kim S, Lo B, Pentz R, Rodriguez L, Weil C, Wilfond B, Wendler D. (2015) Broad Consent for Research With Biological Samples: Workshop Conclusions. *AJOB* 15:9, 34-42

Bardill J, Garrison N. (2015) Naming Indigenous Concerns, Framing Considerations for Stored Biospecimens. The American Journal of Bioethics, 15:9,73-75,

9:25 - 10:10 **Ethics of Randomized Clinical Trials: Clinical Equipoise**
Robert Truog MD
Professor of Medical Ethics, Anaesthesiology & Pediatrics at Harvard Medical School
Director of the Center for Bioethics 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- 10:35 **Break**

10:35-11:20 **Conflicts of Interest**
Steve Joffe MD MPH
Deputy Director Medical Ethics and Health Policy
University of Pennsylvania Perelman School of Medicine

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* 2012; 307(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.

Rosenbaum, L. (2015). Understanding bias--the case for careful study. *The New England Journal of Medicine, 372*(20), 1959.

November 9, 2016 **Session 6: International Research Ethics and Mock IRB**

8:30-9:15 **Ethical Issues in International research: Standard of Care**
Reidar Lie MD PhD
University of Bergen

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

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

10:10- 10:20 **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 (book)
Chapter 68. Fair benefits for Research in Developing countries.

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

Wendler D, Emanuel EJ, Lie RK. The standard of care debate: can research in developing countries be both ethical and responsive to those countries' health needs? Am J Public Health. 2004 Jun;94(6):923-8.

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

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

10:35- 11:20 **Community Engagement and Research with Alaskan Natives**
Stacy Rasmus
Billy Charles

Readings (CD):
Rasmus S. Indigenizing CBPR: Evaluation of a Community-Based and Participatory Research Process Implementation of the Elluam Tungiinun (Towards Wellness) Program in Alaska. *Am J Community Psychol*. Published on-line April 24,2014 DOI 10.1007/s10464-014-9651-5

Rasmus S, Charles B, Mohatt GV. Creating Qungasvik (A Yup'ik Intervention ''Toolbox''): Case Examples from a Community-Developed and Culturally-Driven Intervention. *Am J Community Psychol.* Published on-line April 23, 2014. DOI 10.1007/s10464-014-9653-3

November 16, 2016 Session 7: Ethics of Pragmatic Trials and Incidental Findings

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

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

Readings:
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

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

Collaboratory Case Study, available at >https://www.nihcollaboratory.org/demonstration-projects/Pages/regulatory-ethics.aspx

9:25-9:45 **Break**

9:45-10:20 **How to think about Incidental Findings**
Ben Berkman JD MPH
NHGRI Bioethics Core and NIH Clinical Center Department of Bioethics

10:20- 10:30 **Discussion**

Readings

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)

10:3- 11:30 **Case Discussion**
Ben Berkman