Ethical and Regulatory Aspects of Clinical Research
NIH CC Department of Bioethics
Wednesdays, Sept. 26, 2012- November 7, 2012

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)

September 26, 2012 **Session 1: History, Guidance, and Framework for Ethical Clinical Research**

8:30-8:40 Pre-test

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

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

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

9:30- 10:15 **History, Scandals and Tragedies: Beecher, Tuskegee, Willowbrook and the Rest**
Susan E. Lederer PhD
University of Wisconsin

10:15- 10:25 **Discussion**

Readings:
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.".

10:25-10:40 **Break**

10:40-11:20 **Do the Codes Apply to My Research? Nuremberg, Helsinki, the Belmont Report, CIOMS, and the Common Rule**
Ivor Pritchard PhD
Office of Human Research Protections/DHHS

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

Readings
Chapter 5. The Nuremberg Code
Chapter 6. The Declaration of Helsinki
Chapter 7. The Belmont Report
Chapter 8. The Common Rule

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

October 3, 2012 Session 2: IRB review, Informed Consent and Investigator Panel

8:30-9:15 **Purpose and Function of IRBs: Successes and Current Challenges**
Barbara Karp MD
Chair of CNS and NIDA IRBs/NIH

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

Readings:

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."
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

9:25-10:10 **Informed Consent**
Christine Grady RN PhD
NIH Clinical Center Dept of Bioethics

10:10-10:20 **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?

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.

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

10:35-11:30 **Investigator Panel**
Kathleen Morton RN MSN- NCI
Maryland Pao MD – NIMH
Kristina Rother MD MHSc- NIDDK
Antonio Fojo MD PhD- NCI

<u>October 10, 2012</u> **Session 3: Subject selection, Coercion and Undue inducement, and the ethics of research with children**

8:30-9:15 **Fair Subject Selection**
Dave Wendler PhD
NIH Clinical Center Dept of Bioethics

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

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

9:25- 10:10 **Coercion, Undue inducement, and Incentives in Research**
Alan Wertheimer PhD
NIH Clinical Center Dept of Bioethics

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

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

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

Supplementary readings
Chapter 28, Lemmens T, Elliott C. "Justice for the professional guinea pig"
Chapter 29, McNeill P. "Paying people to participate: why not?"
Emanuel, EJ. Undue Inducement – Nonsense on Stilts. *American Journal of Bioethics* 2005;5(5):9-13.

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

10:35-11:20 **Ethical issues in research with children**
Robert Nelson MD PhD
FDA

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

Readings:
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."
CD
Roth-Cline MD, Gerson J, Bright P, Lee CS, Nelson RM. (In Press) Ethical considerations in conducting pediatric research. In H Seyberth, A Rane, M Schwab, (Eds.) *Pediatric Clinical Pharmacology*. 1st Edition. Springer

<u>October 17, 2012</u> **Session 4: Risks and Benefits, Research with Adults who cannot consent, and Participant Panel**

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

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

Readings
Chapter 42. Freedman B, Fuks A, Weijer C. "*In loco parentis*: Minimal risk as an ethical threshold for research upon children.
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**
Donald Rosenstein, MD
University of North Carolina Medical Center

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

Readings
Chapter 38. National Bioethics Advisory Commission, excerpts from "Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity"
CD
Chen DT, Miller FG, Rosenstein DL. "Enrolling Decisionally Impaired Adults in Clinical Research." *Medical Care*, 2002, Vol. 40(9) 20-29**.**

Supplementary readings

Kim Scott YH, Karlawish Jason HT, Caine Eric D. "Current State of Research on Decision-Making Competence of Cognitively Impaired Elderly Persons." *Am J Geriatric Psychiatry*, 2002; 10(2):151-165**.**
Misra S, Ganzini L. Capacity to consent to research among patients with bipolar disorder. *Journal of Affective Disorders*. 2004; 80:115-123

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

10:35- 11:30 **Participant Panel (TBA)**

October 24, 2012 **Session 5: Ethics and International Research**

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

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

9:25- 10:10 **Ethical Issues in International research**
Joe Millum PhD
NIH Clinical Center Department of Bioethics and Fogarty International Center

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

Readings
Chapter 65. Lurie P & Wolfe S. "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries"
Chapter 66. Annas G & Grodin M. "Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa"
Chapter 68. Participants in the 2001 conference on Ethical Aspects of Research in Developing Countries**.** Fair benefits for Research in Developing countries.

CD
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
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; 189:930-7.

10:20-10:35 Break

10:35- 11:30 mock IRB

Please read the protocol on the CD

<u>October 31, 2012</u> Session 6: Ethics of randomized trials, the use of placebo in trials, and Conflicts of Interest

8:30-9:15 Ethics of Placebo Controlled Trials
Frank Miller, PhD
NIH Clinical Center Department of Bioethics

9:15- 9:25 Discussion

Readings:
Chapter 17. Freedman B. "Placebo-Controlled trials and the logic of clinical purpose"
Chapter 19. Emanuel EJ, Miller FG. "The Ethics of Placebo-Controlled Trials – A Middle Ground."
Chapter 16. Rothman K, Michels K. "The continuing unethical use of placebo controls."
Chapter 18. Temple R, Ellenberg S. "Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments, Part 1: Ethical and Scientific Issues."

9:25- 10:10 Ethics of Randomized Clinical Trials: Clinical Equipoise
Robert Truog MD
Harvard Medical School

10:05-10:20 Discussion

Readings
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
Dana Farber Cancer Institute and Harvard Medical School

11:20- 11:30 Discussion

Readings

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."

CD
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**
Lexchin J, Bero L, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. ***BMJ* 2003; 326: 1167-11701.**
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.

November 7, 2012 Session 7: The Research Use of Stored Tissue and Data, and Incidental Findings in 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

Readings

Caulfield T, McGuire AL, Cho M, Buchanan JA, Burgess MM, et al. (2008) Research ethics recommendations for whole-genome research: Consensus statement. *PLoS Biol* 6(3): 430-435

Giesbertz NAA, Bredenoord AL, van Delden JJM (2012) Inclusion of Residual Tissue in Biobanks: Opt-In or Opt-Out? *PLoS Biol* 10(8): e1001373. doi:10.1371/journal.pbio.1001373

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

Emanuel E, Menikoff J. Reforming the Regulations Governing Research with Human Subjects *NEJM* ; 2011 Jul 25 (See Session 1)

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

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

Readings:

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,1 R Christensen,1 M Giacomini,2,3 J S Robert4,5 Duty to disclose what? Querying the putative obligation to return research results to participants *J Med Ethics* 2008. 34: 210-213

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

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

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