Ethical and Regulatory Aspects of Clinical Research
NIH CC Department of Bioethics
Wednesdays, September 30- November 18, 2015
Syllabus with Readings

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 or Amazon)

September 30, 2015 **Session 1: History and Framework for Ethical Clinical Research**

8:30-8:40 **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

9:40-9:55 **Break**

9:55- 10:40 **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

10:40- 10:50 **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.

10:50- 11:30 **Update on Federal Regulations**
Carrie Wolinetz PhD
Director, NIH Office of Science Policy

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 7, 2015 **Session 2: Fair subject selection, community engagement and voices**

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

9:15-9:25 **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.

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

9:40-11:00 **Ethics of Community Engagement**
(NIMHD Sponsored Session)
CBPR Investigators and Community Partners

(9:40- 10:10) Carol Horowitz MD, MPH
Associate Professor
Co-Director, Center of Health Equity and Community Engaged Research
Department of Population Health Science and Policy Department of Medicine
Icahn School of Medicine at Mount Sinai

Crispin Noelle Goytia, BA
Community and Patient Engagement Specialist
East Harlem Diabetes Center of Excellence
Icahn School of Medicine at Mount Sinai

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(10:10- 10:35) Brian Mustanski, PhD
Associate Professor, Department of Medical Social Sciences
Director, IMPACT Program
Co-Director, Third Coast Center for AIDS Research (CFAR)
Northwestern University, Feinberg School of Medicine

Dr. Héctor Torres
Director of Behavioral Health
Center on Halsted

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(10:36-11:00) Moon S. Chen Jr. MPH, PhD
Professor, Div. of Hematology & Oncology, Department of Internal Medicine,
Principal Investigator, AANCART: The National Center for Reducing Asian American Cancer Health Disparities
Associate Director for Cancer Control, UC Davis Comprehensive Cancer Center

Ms. Kendra Thao
Executive Director
Hmong Women's Heritage Association

11:00-11:30 **Panel Q&A**

READINGS

Pacheco CM, Daley SM, Brown T, Filippi M, Greiner KA, Dale CM. Moving forward: breaking the cycle of mistrust between American Indians and researchers. *American Journal of Public Health* (2013) 103:2152-9. http://ajph.aphapublications.org/doi/full/10.2105/AJPH.2013.301480

Getrich CM, Sussman AL, Campbell-Voytal K, Tsoh JY, Williams RL, Brown AE, Potter MB, Spears W, Weller N, Pascoe J, Schwartz K, Neale AV. Cultivating a Cycle of Trust with Diverse Communities in Practice-Based Research: A Report from PRIME Net. *Annals of Family Medicine* (2014) 11:550-8.

Chen, MS, Lara, PN, Dang JHT, Paterniti, DA, Kelly, K. Twenty years post-NIH Revitalization Act: Enhancing minority participation in clinical trials (EMPaCT): Laying the groundwork for improving minority clinical trial accrual. *Cancer* (2014) 120:1091-1096.

Mikesell, L, Bromley E, Khodyakov, D. Ethical Community-Engaged Research: A Literature Review *Am J Public Health* (2013) 103 (12):e7-e14.

Mustanski Ethical and Regulatory Issues with Conducting Sexuality Research with LGBT Adolescents: A Call to Action for Scientifically Informed Approach. (2011) *Arch Sex Behav* 40:673-686.

Anderson, EE et.al, Research Ethics Education for Community-engaged Research: A Review and Research Agenda. *Journal Empirical Research Human Research Ethics* (2012) 7(2):3-19

George S, Duran N, and Norris K. Systematic Review of Barriers and Facilitators to Minority Research Participation. *American Journal of Public Health*: (2014) 104 (2): e16-e31. http://ajph.aphapublications.org/doi/full/10.2105/AJPH.2013.301706

October 14, 2015 **Session 3: IRBs, Risk and Benefits, and Informed Consent**

8:30- 9:15 **Purpose and Function of IRBs: Successes and Current Challenges**
Sara Hull PhD
Chair, NHGRI IRB

9:15-9:25 **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

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

9:25- 10:10 **Risks and Benefits**
Dave Wendler, PhD
NIH Clinical Center Department of Bioethics

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.

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

10:20-10:35 Break

10:35-11:20 **Informed Consent**
Christine Grady RN PhD
NIH Clinical Center Dept of Bioethics

11:20-11:30 **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 (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.

October 21. 2015 **Session 4: Research involving persons at risk for impaired decision making, Ethical issues in stored tissue research, and incidental findings**

8:30-9:15 **Research Involving Persons at Risk for Impaired Decision-Making**
Scott Kim MD PhD
NIH Clinical Center Department of Bioethics

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

Readings: (book and online)
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; 161:797–806*

Supplementary readings

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

9:25- 10:10 **Ethical Issues in the Use of Stored Tissue and Data**
Sara Chandros Hull PhD
NHGRI and NIH Clinical Center Department of Bioethics

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

Readings:

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,

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

10:35- 11:20 **How to think about Incidental Findings**
Ben Berkman JD
NHGRI Bioethics Core and NIH Clinical Center Department of Bioethics

11:20-11:30 **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)

October 28, 2015 **Session 5: International Research Ethics and Conflicts of Interest**

8:30-9:15 **Ethical Issues in International research**
Joe Millum PhD
NIH Clinical Center Department of Bioethics and Fogarty International Center

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

9:25- 10:10 **Ethical issues in International Research**
Seema Shah JD
NIH Clinical Center Department of Bioethics and NIAID Division of AIDs

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

Readings on International Research Ethics:

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.

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

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 Unintedend 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.

<u>Nov. 4, 2015</u> Session 6: Ethics of Research with Children, Ethics of Randomized Trials, and mock IRB

8:30-9:15 **Ethics of Research with Children**
Robert "Skip" Nelson MD
Director of Ethics and Deputy Director,
Office of Pediatric Therapeutics
US Food and Drug Administration

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,"
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

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

Professor of Medical Ethics, Anesthesiology & Pediatrics at Harvard Medical School
Harvard University Program in Ethics and Health

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**

10:35-11:30 **Mock IRB**
Christine Grady

PLEASE READ the Protocol on the CD before Nov. 4

November 11, 2015- FEDERAL HOLIDAY, NO CLASS

November 18, 2015 **Session 7: Special Topics in Research Ethics**

8:30-9:15 **The Ethics of Challenge Studies**
Seema Shah JD
NIH Clinical Center Department of Bioethics and NIAID Division of AIDs

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

Readings (CD):

Franklin G. Miller and Christine Grady, "The Ethical Challenge of Infection-Inducing Challenge Experiments," *Clinical Infectious Diseases* 33 (2001): 1028-33.

Lynch HF, The rights and wrongs of intentional exposure research: contextualising the Guatemala STD inoculation study. J Med Ethics. 2012 Aug;38(8):513-5. doi: 10.1136/medethics-2011-100379. Epub 2012 Mar 19.

Letters to the Editor regarding Willowbrook. Lancet. 1991

9:25-10:10 **Ethics of Research with Pregnant women**
Maggie Little PhD

Director of the Kennedy Institute of Ethics, and Associate Professor of Philosophy

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

Readings:
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
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

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

10:35- 11:30 **Pragmatic Trials Case Discussion**
Scott Kim MD PhD
NIH Clinical Center Department of Bioethics

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