Ethical and Regulatory Aspects of Clinical Research
NIH CC Department of Bioethics
Wednesdays, September 26-November 7, 2018

<u>September 26, 2018</u> **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: (book)
Chapter 5. The Nuremberg Code
Chapter 6. The Declaration of Helsinki
Chapter 7. The Belmont Report

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 **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

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

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

Hellman S, Hellman D. Of Mice But Not Men: Problems of the Randomized Clinical Trial. *NEJM* 1991

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

10:40- 11:20 **Purpose and Function of IRBs: Successes and Current Challenges**
Sara Hull PhD
Chair, NHGRI IRB
Director, NHGRI Bioethics Core

11:20-11:30 **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:
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. Institutional Review Boards: Purpose and Challenges. *Chest*. 2015 Nov 1; 148(5):1148-55

October 3, 2018 **Session 2: Risks and Benefits, and the Ethics of Research with Children**

8:30-9:15 **Risks and Benefits**
Dave Wendler PhD
Head of Section on Ethics and Research
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:
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- 9:40 **Break**

9:40-10:25 **Ethics of Research with Children**
Alan Fleischman MD
Professor, Department of Pediatrics (Neonatology)
Professor, Department of Epidemiology & Population Health
Albert Einstein College of Medicine

10:25-10:35 **Discussio**n

Readings:

Readings: (these are from the Emanuel, Crouch, et al. anthology 2003)
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:
Fleischman, A.R. and Collogan, L.: Research with Children, in: The Oxford Textbook of Clinical Research Ethics. (eds) EJ Emanuel, C Grady, RA Crouch, R Lie, F Miller, and D Wendler, Oxford University Press, 446-460, 2008

10:40- 11:30 **Review of a protocol**
Alan Fleischman MD
Professor, Department of Pediatrics (Neonatology)
Professor, Department of Epidemiology & Population Health
Albert Einstein College of Medicine

<u>October 10, 2018</u> **Session 3: Research with Samples and Data, Big Data, and Incidental Findings**

8:30-9:15 **Incidental and secondary Findings**
Ben Berkman JD MPH
NHGRI Bioethics Core and NIH Clinical Center Department of Bioethics

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

Readings:
Wolf S et al. Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations 2008. *J Law, Med & Ethics*

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

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)

9:25-10:10 **Research with Biospecimens and Data Under the Revised Common Rule**

Holly Fernandez Lynch, JD, MBe
John Russell Dickson MD Presidential Assistant Professor of Medical Ethics
Assistant Faculty Director of Online Education
Department of Medical Ethics and Health Policy
Perelman School of Medicine, University of Pennsylvania

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. *The American Journal of Bioethics* 15:9, 34-42.

Lynch HF, Meyer MN. (2017) Regulating Research with Biospecimens under the Revised Common Rule, *Hastings Ctr Rep*, 47:3-4.

Suzanne M Rivera and Heidi Aungst, What Specimen Donors Want (and Considerations That May Sometimes Matter More) in *Specimen Science: Ethics and Policy Implications* (MIT Press, 2017).

SACHRP Broad Consent Recommendations and Template
https://www.hhs.gov/ohrp/sachrp-committee/recommendations/sachrp-recommendations/index.html

10:20-10:35 **BREAK**

10:35- 11:30 **Research with Big Data**
Jeff Kahn PhD
Andreas C. Dracopoulos Director
Johns Hopkins University Berman Institute of Bioethics

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

Readings:
Effy Vayena, Marcel Salathé, Lawrence C. Madoff, John S. Brownstein, (2015) "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, (2014). "Learning as We Go: Lessons from the Publication of Facebook's Social-computing Research," *Proc Natl Acad Science* 111(38):13677-13679; 2014; doi: 10.1073/pnas.1416405111.

October 17, 2018 **Session 4: Fair Subject Selection, the History of Research Ethics, Research with Native Americans and Alaskan Natives**

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

MacKay D, Fair subject selection in clinical research: formal equality of opportunity. *J Med Ethics* doi: 10.1136/medethics-2015-103311

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.

9:25-10:10 **History, Scandals and Tragedies: Beecher, Tuskegee, Willowbrook and the Rest**
Jonathan D. Moreno PhD
David and Lyn Silfen University Professor
Department of Medical Ethics and Health Policy
Department of History and Sociology of Science

University of Pennsylvania

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

Readings:

Readings: (our 2003 book)
Chapter 3. Beecher, H. "Ethics and clinical research."

Readings:

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.

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

10:35- 11:20 **Community Based Research with American Indian and Alaskan Native Tribes**
David R. Wilson, Ph.D.
Director, Tribal Health Research Office (THRO)
NIH

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

Readings:

<u>October 24, 2018</u> **Session 5: Ethics of Randomized Clinical Trials, and Ethics of Pragmatic Trials, AND Ethical issues in *All of Us***

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. 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: (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

10:35-11:20 ***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.

<u>October 31, 2018</u> **Session 6: Informed consent, research with those with impaired capacity for consent, and participant panel**

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:
Nishimura A, Carey J, Erwin P, Tilburt J, Murrad MH, McCormick J. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. *BMC Medical Ethics* 2013, 14:28

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
Senior Investigator
Department of Bioethics, NIH Clinical Center

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

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- 11:30 **Participant Panel**

November 7, 2018 **Session 7: Ethical issues in international research**

8:30-9:15 **Ethical Issues in International research: Introduction and Standard of Care**

Annette Rid MD
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**

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

10:35-11:30 **Case discussion**
Joe Millum and Annette Rid

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/

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

Lie, Reidar 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, Christine. "The challenge of assuring continued post-trial access to beneficial treatment." *Yale J. Health Pol'y L. & Ethics* 5 (2005): 425.

Millum, Joseph. "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, Rebecca, Ezekiel Emanuel, and Seema Shah. "Rethinking the responsiveness requirement for international research." *The Lancet* 374.9692 (2009): 847-849.

El Setouhy, M., et al. "Ethics: Fair benefits for research in developing countries: Participants in the 2001 conference on ethical aspects of research in developing countries." *Science* 298.5601 (2002): 2133-2134.