Ethical and Regulatory Aspects of Clinical Research Ethics

September 23 to November 4, 2020
8:30-11:30 am
All material to be delivered by NIH Videocast and CANVAS

9.22.20 MASTER

OVERVIEW

Date	**Session**	**Faculty**
September 23	Session 1: Ethical Framework/ Risk Benefit Assessment	Holly Taylor Christine Grady David Wendler
September 30	Session 2: Informed Consent/Privacy and Confidentiality	Christine Grady Scott Kim Ben Berkman Holly Taylor
October 7	Session 3: Subject Selection	Holly Taylor Dave Wendler *Camila Strassle*
October 14	Session 4: Genetics	Ben Berkman Leila Jamal Sara Hull *Katrina Claw* Holly Taylor
October 21	Session 5: IRBs/Trial Design	*Robert Troug* Scott Kim Sara Hull Holly Taylor
October 28	Session 6: International Research	Joe Millum Maria Merritt *Dorcas Kamuya*
November 4	Session 7: COVID	Christine Grady *Nir Eyal* *Seema Shah* Annette Rid Holly Taylor *Anne Barnhill*

Overall Course Objectives

Upon completion of this course, you should be able to:

By the end of this course, participants are able to:

- Utilize a systematic framework for evaluating the ethics of a clinical research protocol.
- Identify, define and consider ethical issues in the conduct of human subject research.
- Apply appropriate codes, regulations, and other documents governing the ethical conduct of human subject research to their own research.
- Identify the critical elements of informed consent and strategies for implementing informed consent for clinical research.
- Describe the purpose, function, and challenges of IRBs.
- Discuss controversial issues relating to human subject research, including, randomization, prisoners in research, COVID related research, international research, etc…

Session 1: Ethical Framework, Risk Benefit Wednesday September 23

Objectives:

- Identify and describe the ethical principles and historical basis that provide guidance for the ethical conduct of research.
- Describe important cases in the history of research and how cases shaped current ethical considerations, and regulations for clinical research.
- Describe ethical framework to be applied throughout course
- Identify and apply relevant considerations for assessment of research risks and benefits

Time	Topic	Faculty
8:30-8:40	Introduction to Course	Holly Taylor PhD MPH NIH Clinical Center Department of Bioethics
8:40-10:10	Framework for Ethical Conduct of Research	Christine Grady RN PhD NIH Clinical Center Department of Bioethics Holly Taylor PhD MPH NIH Clinical Center Department of Bioethics
10:10-10:20	Discussion	
10:20-10:35	Break	
10:35-11:20	Risk/Benefit	Dave Wendler PhD NIH Clinical Center Department of Bioethics
11:20-11:30	Discussion	

Textbook Reading Assignment

Part I: Scandals and Tragedies of Research with Human Participants: Nuremberg, the Jewish Chronic Disease Hospital, Beecher and Tuskegee (Overview and Chapters 1-4; pp. 1-23)

Part II: Ethical and Regulatory Guidance for Research with Humans (Overview and Chapters 5-7; pp. 25-38)

Part VI: Clinical Research with Special Populations (Chapter 42; pp. 247-252)

Additional Readings

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

Rid A, Emanuel E, Wendler D. Evaluating the Risks of Clinical Research. *JAMA*. 2010; 304(13):1472-1479

Optional

Video – The Deadly Deception (Tuskegee Syphilis Study). NOVA Season 20, Episode 14, January 26, 1993. Posted on CANVAS, not great quality.

Session 2: Informed Consent/Privacy and Confidentiality Wednesday September 30

Objectives:

- Describe the ethical basis of and elements of informed consent, strategies for implementation, and areas for improvement.
- Identify the ethical challenges of including persons in research who have decreased capacity to consent, and discuss the implementation of appropriate additional safeguards Understand the barriers and facilitators to obtaining informed consent from research participants
- Experience drafting key components of informed consent form

Time	Topic	Faculty
8:30-9:15	Informed Consent	Christine Grady RN PhD NIH Clinical Center Department of Bioethics
9:15-9:25	Discussion	
9:25-10:05	Research Involving Persons at Risk for Impaired Decision-Making	Scott Kim MD PhD Department of Bioethics, NIH Clinical Center
10:05-10:15	Discussion	

10:15-10:30	Break	
10:30-10:50	Privacy and Confidentiality	Holly Taylor PhD MPH NIH Clinical Center Department of Bioethics
10:50-11:20	Repurposing Biospecimens for COVID Research	Ben Berkman, JD NIH Clinical Center Department of Bioethics and NHGRI
11:20-11:30	Discussion	

Textbook Reading Assignment

Part V: Informed Consent in Research (Overview and Chapters 30-33; pp. 189-210)

Part VI: Clinical Research with Special Populations (Chapter 38; pp. 229-233)

Part VII. Special Topics in Research Ethics (Chapter 54; pp. 311-312)

Additional Readings

Grady C. Enduring and Emerging Challenges of Informed Consent, *New Eng J Med*, 2015;372 (9):855-62.

Kim SY, 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.* 2011 May 24; 7(7): 410–414.

NIH Policy - Research Involving Adults Who Lack Decision-making Capacity to Consent to Research Participation September 14, 2020

Session 3: Subject Selection Wednesday October 7

Objectives:

- Explore the ethical requirement of fair subject selection and its application
- Identify ethical issues and strategies in the recruitment and retention of subjects.
- Review ethical challenges and strategies for conducting ethical research involving prisoners

Time	**Topic**	**Faculty**
8:30-9:10	Fair Subject Selection	Holly Taylor PhD MPH NIH Clinical Center Department of Bioethics
9:10-9:50	Recruitment and Retention	Dave Wendler PhD

		NIH Clinical Center Department of Bioethics
9:50-10:05	Break	
10:05-10:30	Enrollment of Prisoners: Key Considerations	Holly Taylor *in Conversation with* Camila Strassle, Stanford Law School
10:30-10:40	Discussion	
10:40-11:30	Case Discussion: Lead-Based Paint Abatement and Repair and Maintenance Study	Holly Taylor/Dave Wendler

Textbook Reading Assignment

Part I: Scandals and Tragedies of Research with Human Participants: Nuremberg, the Jewish Chronic Disease Hospital, Beecher and Tuskegee (Chapters 4; pp. 20-23)

Pat II: Clinical Research with Special Populations (Chapter 45; pp. 262-266)

Part IV: The Ethics of Research Participant Recruitment (Chapter 22; pp. 155-166, Chapters 24-25; pp. 166-175, Chapter 27; pp. 179-183, Chapter 29; pp. 185-188)

Part VIII: The Behavior of Clinical Investigators: Conflicts of Interest (Chapter 73; pp. 377-378)

Session 4: Genetics Wednesday October 14

Objectives:

- Identify challenges and opportunities related to genetics research and research with stored samples
- Understand how the rapid development and diffusion of genetic technology influence the conduct of human subject research
- Understand the difference between research findings and incidental findings and the relevant ethical considerations for each
- Appreciate the complexity of conducting genetics research with native populations
- Understand the concept of group harms

Time	**Topic**	**Faculty**
8:30-10:15	Ethics of Genetics Research and Incidental Findings	Ben Berkman, JD, MPH NIH Clinical Center Department of Bioethics and NHGRI Lelia Jamal, PhD, ScD, CGC NIH Clinical Center Department of Bioethics and NCI

10:15-10:30	Break	
10:00-10:30	Enrollment of Native Populations: Key Considerations	Sara Hull *in Conversation* with Katrina Claw University of Colorado Anschutz Medical Campus
10:30-10:40	Discussion	
10:40-11:30	Case Discussion: Arizona State University Diabetes Project	Sara Hull/Holly Taylor

Readings

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

All of Us Research Program Investigators, et al. The "All of Us" Research Program. *N Engl J Med.* 2019 Aug 15; 381(7):668-676.

Claw KG, Anderson MZ, Begay RL, Tsosie KS, Fox K, Summer internship for Indigenous Peoples in Genomics (SING) Consortium & Garrison NA. A Framework for Enhancing Ethical Genomic Research with Indigenous Communities. *Nature Communications* 2018; 1-6. DOI: 10.1038/s41467-018-05188-3

Session 5: Trial Design/IRBs Wednesday October 21

Objectives:

- Identify ethical issues in the design and conduct of randomized controlled trials, and explore meanings and issues related to clinical equipoise Understand the basis of the role and responsibilities of an Institutional Review Board
- Discuss ethical considerations in the design and conduct of pragmatic clinical trials.
- Discuss the purpose and function of IRBs, and current challenges

Time	**Topic**	**Faculty**
8:30-9:15	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
9:15-9:25	Discussion	
9:25-10:10	Pragmatic Trials	Scott Kim MD PhD Senior Investigator NIH Clinical Center Department of Bioethics

10:10-10:25	Discussion	
10:25-10:40	Break	
10:40-11:20	IRBs	Holly Taylor, PhD, MPH NIH Clinical Center Department of Bioethics Sara Hull, PhD NIH Clinical Center Department of Bioethics and NHGRI
11:20-11:30	Discussion	

Textbook Reading Assignment

Part III: The Ethics of Trial Design (Chapter 11; pp. 103-107, Chapters 13-15; pp. 113-126)

Part X: Challenges to the Institutional Review Board System (Chapter 85; pp-436-440)

Additional Readings

Kim SY. Ethical Issues in Pragmatic Trials of "Standard-of-Care" Interventions in Learning Health Care Systems. *Learn Health Sys*. 2017:1-5.

Kim SY & Miller FG. (2015). Varieties of Standard-of-Care Treatment Randomized Trials: Ethical Implications. *JAMA*, 313(9), 895-896.

Common Rule, 45 CFR 46 (2018) https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML

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

Session 6: International Research Wednesday October 28

Objectives:

- Appreciate challenges with conducting human subject research in low and middle income countries
- Understand the meaning of standard of care in the context of human subject research
- Understand the obligations investigators, sponsors have to research participants after trial completion (e.g. post-trial access)
- Apply IRB assessment tool to research proposal

Time	Topic	Faculty

8:30-8:55	Introduction and Standard of Care	Joseph Millum PhD NIH Clinical Center Department of Bioethics and Fogarty International Center
8:55-9:10	Discussion	
9:10-9:35	Ancillary Care Obligations	Maria Merritt PhD Visiting Scholar NIH Clinical Center Department of Bioethics Johns Hopkins Bloomberg School of Public Health Johns Hopkins Berman Institute of Bioethics
9:35-9:50	Discussion	
9:50-10:05	Break	
10:05-10:35	Perspectives from Kenya	Joe Millum *in Conversation* with Dorcas Kamuya, PhD, MPH Head of Health Systems and Research Ethics KEMRI-Wellcome Trust Research Programme Nairobi, Kenya
10:35-11:30	Mock IRB: Study *TBA*	Joe Millum/Holly Taylor

Readings

Adebamowo C, et al. "Randomised Controlled Trials for Ebola: Practical and Ethical issues." *The Lancet* 2014; 384(9952): 1423-1424.

Wendler D, Emanuel EJ, and Lie RK. "The Standard of Care Debate: Can Research in Developing Countries be Both Ethical and Responsive to Those Countries' Health Needs?" *American Journal of Public Health* 2004; 94 (6): 923-928.

Council for International Organization of Medical Sciences (CIOMS). International Ethical Guidelines for Health-related Research Involving Humans (2016) https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/
Guideline 2. Research conducted in low-resource settings.
Guideline 5. Choice of control in clinical trials.

World Medical Association. Declaration of Helsinki (2013) https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Participants in the 2006 Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries (Brownsword R, Cermak A, Chaisson R, Clayman MD, Corr PB, DeCherney S, Grady C, Higgs ES, Kumar NK, Lie R, Merritt M,

Molyneux M, Petros B, Richardson HS, Sugarman J), The Ancillary-Care Obligations of Medical Researchers Working in Developing Countries," *PLoS Medicine* 2008; 5(5): e90.

Optional:

Merritt MW, "Health Researchers' Ancillary Care Obligations in Low-Resource Settings: How Can We Tell What Is Morally Required?" K*ennedy Institute of Ethics* Journal 2011; 21 (4): 311-347.

Session 7: COVID Vaccines Wednesday November 4

Objectives:

- Explore key course topics in the context of COVID
- Appreciate differences in methods and strategies, and the associated ethical challenges in testing experimental vaccines.

Time	Topic	Faculty
8:30-9:00	Approaches to Vaccine Trial Design	Christine Grady RN PhD NIH Clinical Center Department of Bioethics
9:00-10:00	Ethics of Controlled Human Infection Trials	Seema Shah, JD Northwestern University Nir Eyal, PhD Rutgers Moderator: Annette Rid MD, PhD NIH Clinical Center Department of Bioethics and NIAID
10:00-10:15	Break	
10:15-10:35	Obligations to COVID Vaccine Research Subjects	Holly Taylor, PhD, MPH NIH Clinical Center Department of Bioethics
10:35-10:45	Discussion	
10:45-11:20	Vaccine Dissemination	Anne Barnhill, PhD Research Scholar Berman Institute of Bioethics Johns Hopkins University
11:20-11:30	Discussion	

Readings

Grady C, Shah S, Miller F, Danis M, Nicolini M, Ochoa J, Taylor HA, Wendler D, Rid A. So Much at Stake: Ethical Tradeoffs in Accelerating SARSCoV-2 Vaccine Development. *Vaccine* 2020; 38(41): 6381-6387.

WHO Working Group for Guidance on Human Challenge Studies in COVID-19
Key criteria for the ethical acceptability of COVID-19 human challenge studies. 2020
https://www.who.int/ethics/publications/key-criteria-ethical-acceptability-of-covid-19-human-challenge/en/

Persad G, Peek ME, Emanuel E. Fairly Prioritizing Groups for Access to COVID-19 Vaccines. *JAMA* Published on-line September 11, 2020.

Toner E, Barnill A, Krubiner C, et al. *Interim Framework for COVID-19 Vaccine Allocation and Distribution in the United States*. Baltimore, MD: Johns Hopkins Center for Health Security; 2020.