Ethical and Regulatory Aspects of Clinical Research

September 22 to November 3, 2021
8:30-11:30 am
All material to be delivered by NIH Videocast and CANVAS

8.3.21

OVERVIEW

Session	Date	Topics	Faculty
1	9/22/21	Ethical Framework/ Physician-Investigator Role/History of Research Ethics	Taylor, Grady, *Joffe*
2	9/29/21	Randomized Clinical Trials/ Risk-Benefit/Institutional Review Boards	Wendler, *Truog,* Taylor
3	10/6/21	Subject Selection/Inclusion of Pregnant Women/Recruitment and Retention	Wendler, *Lyerly,* Taylor
4	10/13/21	Informed Consent/Decision Making/Capacity Assessment	Grady, Kim, Todman, Taylor
5	10/20/21	Returning Results/Incidental Findings/ Collaborating with Indigenous Communities	Berkman, Jamal, Hull, *Claw* and Taylor
6	10/27/21	Vaccines	Grady, Rid, *Langford*
7	11/3/21	International Research/Standard of Care/Post-trial Obligations	Millum, Rid, *Kamuya*

Overall Course Objectives

Upon completion of this course, you should be 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, enrollment of pregnant women in research, COVID related vaccine research, and research conducted in low and middle income countries.

Session 1: Ethical Framework/Physician-Investigator Role/ History of Research Ethics

- September 22

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
- Appreciate the challenges of navigating the roles of physician and investigator (e.g. conflicts of commitment)

Time	**Topic**	**Faculty**
8:30-8:45	Introduction to Course	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics
8:45-9:30	Framework for Ethical Conduct of Research	Christine Grady, RN PhD NIH Clinical Center Department of Bioethics
9:30-9:40	Discussion	
9:40-10:30	Physician/Investigator Roles	Steve Joffe, MD MPH Interim Chair, Department of Medical Ethics & Health Policy Art and Ilene Penn Professor of Medical Ethics & Health Policy University of Pennsylvania
10:30-10:40	Break	
10:40-11:20	Conversation about History of Research Ethics	Christine Grady and Holly Taylor
11:20-11:30	Discussion	

Readings Assignment

Textbook

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. 1-25)

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

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

Morain SR, Joffe S, Largent EA. When Is It Ethical for Physician-Investigators to Seek Consent From Their Own Patients? *American Journal of Bioethics* 2019;19(4):11-18.

Optional

Joffe S & Miller F. Bench to Bedside: Mapping the Moral Terrain of Clinical Research. *Hastings Center Report* 2008; 38(2):30-42.

Session 2: Randomized Clinical Trials/Risk-Benefit/Institutional Review Boards - September 29

Objectives:

- Identify ethical issues in the design and conduct of randomized controlled trials, and explore meanings and issues related to clinical equipoise
- Identify and apply relevant considerations for assessment of research risks and benefits
- Understand the basis of the role and responsibilities of an Institutional Review Board
- Discuss the purpose and function of IRBs, and current challenges

Time	Topic	Faculty
8:30-9:25	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
9:25-9:35	Discussion	
9:35-10:20	Risk/Benefit	David Wendler, PhD NIH Clinical Center Department of Bioethics
10:20-10:30	Discussion	
10:30-10:45	Break	
10:45-11:20	Institutional Review Boards (IRBs)	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics
11:20-11:30	Discussion	

Readings Assignment

Textbook

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

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

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

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

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

Common Rule, 45 CFR 46 (2018) https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/revised-common-rule-regulatory-text/index.html

Optional

Strauss DH, White SA, Bierer BE. Justice, Diversity, and Research Ethics Review. *Science* 2021;371(6535):1209-1211.

Session 3: Subject Selection/Inclusion of Pregnant Women/Recruitment and Retention - October 6

Objectives:

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

Time	Topic	Faculty
8:30-9:10	Fair Subject Selection	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics
9:10-9:20	Discussion	
9:20-10:20	Inclusion of Pregnant Women	Anne Drapkin Lyerly, MD, MA Professor, Department of Social Medicine Center for Bioethics University of North Carolina at Chapel Hill
10:20-10:35	Break	
10:35-11:05	Recruitment and Retention	Dave Wendler, PhD NIH Clinical Center Department of Bioethics
11:05-11:15	Discussion	
11:15-11:30	Mini Case Discussion: TBA	Holly Taylor, PhD MPH

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)

Lyerly AD, Little MO, Faden R. The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research. *International Journal of Feminist Approaches to Bioethics* 2008;1(2):5-2

Beigi RH, Krubiner C, Jamieson DJ, Lyerly AD, Hughes B, Riley L, Faden R, Karron R. The Need for Inclusion of Pregnant Women in COVID-19 Vaccine Trials. *Vaccine*. 2021;39(6):868-870

Optional

The PHASES Working Group. Ending the Evidence Gap for Pregnant Women around HIV & Co-infections: A Call to Action. Chapel Hill, NC: July, 2020.

Session 4: Informed Consent/Decision Making/Capacity Assessment - October 13

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 practice of implementing appropriate safeguards

Time	Topic	Faculty
8:30-9:15	Informed Consent	Christine Grady, RN PhD NIH Clinical Center Department of Bioethics
9:15-9:25	Discussion	
9:25-10:10	Research Involving Persons at Risk for Impaired Decision-Making	Scott Kim, MD PhD NIH Clinical Center Department of Bioethics
10:10-10:20	Discussion	
10:20-10:35	Break	

10:35-11:20	Capacity Assessment in Practice	Katherine Todman MSW, LCSW-C Human Subjects Protection Unit National Institute of Mental Health Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics
11:20-11:30	Discussion	

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)

Journal Articles

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

Scott Y. H. Kim. Chapter 8: Capacity to Consent to Research, from Evaluation of Capacity to Consent to Treatment and Research. Oxford University Press 2010

NIH Policy - Research Involving Adults Who Lack Decision-making Capacity to Consent to Research Participation 2021 https://policymanual.nih.gov/3014-403

Session 5: Incidental Findings/Return of Results/Inclusion of Native Populations- October 20

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**

8:30-9:15	Ethics of Genetics Incidental Findings	Ben Berkman, JD MPH NIH Clinical Center Department of Bioethics and NHGRI
9:15-9:25	Discussion	
9:25-10:05	Returning Research Results in the Context of Evolving Science	Leila Jamal, PhD ScM, CGC NIH Clinical Center Department of Bioethics and NCI
10:05-10:15	Discussion	
10:15-10:30	Break	
10:00-10:30	Enrollment of Native Populations: Key Considerations	Sara Hull, PhD NIH Clinical Center Department of Bioethics and NHGRI *in Conversation* with: Katrina Claw, PhD Assistant Professor – Medicine and Bioinformatics University of Colorado Denver Anschutz Medical Campus
10:30-10:40	Discussion	
10:40-11:30	Case Discussion: Arizona State University Diabetes Project	Sara Hull and Holly Taylor

Reading Assignment

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. *NEJM.* 2019; 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.

Garrison NA, Hudson M, Ballantyne LL, Garba I, Martinez A, Taualii M, Arbour L, Caron NR, Rainie SC. Genomic Research Through an Indigenous Lens: Understanding the Expectations. *Annual Review of Genomics and Human Genetics* 2019;20:495-517.

Session 6: Vaccines - October 27

Objectives:

- Appreciate ethical challenges in testing experimental vaccines and how COVID has changed the enterprise
- Understand the unique challenges in conducting controlled human infection trials
- Appreciate how attention to equitable inclusion in vaccine trials can reduce vaccine hesitancy and uptake

Time	Topic	Faculty
8:30-9:15	Vaccine Development: The Case of COVID	Christine Grady, RN PhD NIH Clinical Center Department of Bioethics
9:15-9:25	Discussion	
9:25-10:10	Ethics of Controlled Human Infection Trials	Annette Rid, MD PhD NIH Clinical Center Department of Bioethics and NIAID
10:10-10:20	Discussion	
10:20-10:35	Break	
10:35-11:30	What does Equitable Inclusion have to do with Addressing Vaccine Hesitancy?	Aisha Langford, PhD MPH Department of Population Health Co-Director, CTSI Recruitment and Retention Core NYU Grossman School of Medicine

Reading Assignment

Grady C. Ethics of Vaccine Research. *Nature Immunology* 2004;5(5):465-8.

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.

Shah SK, Miller FG, Darton TC, Duenas D, Emerson C, Lynch HF, Jamrozik E, Jecker NS, Kamuya D, Kapulu M, Kimmelman J, MacKay D, Memoli MJ, Murphy SC, Palacios R, Richie TL, Roestenberg M, Saxena A, Saylor K, Selgelid MJ, Vaswani V, Rid A. Ethics of Controlled Human Infection to Address COVID-19. *Science* 2020;368(6493):832-834.

Langford AT, Bateman-House A. Clinical Trials For COVID-19: Populations Most Vulnerable To COVID-19 Must Be Included. Health Affairs Blog 2020 https://www.healthaffairs.org/do/10.1377/hblog20200609.555007/full/

Fisher J. Inclusive Vaccine Trials Are Vital, But Let's Not Boost Biological Views of Race. Op-ed Truthout 2020 https://truthout.org/articles/inclusive-vaccine-trials-are-vital-but-lets-not-boost-biological-views-of-race/

Optional:

Langford A. Health Communication and Decision Making about Vaccine Clinical Trials during a Pandemic. *Journal of Health Communications* 2020; 25(10): 780-789.

Jamrozik E, Littler K, Bull S, Emerson C, Kang G, Kapulu M, Rey E, Saenz C, Shah S, Smith PG, Upshur R, Weijer C, Selgelid MJ; WHO Working Group for Guidance on Human Challenge Studies in COVID-19.Key criteria for the ethical acceptability of COVID-19 human challenge studies: Report of a WHO Working Group *Vaccine* 2021, 39(4): 633-640.

Session 7: November 3 – International/Standards of Care/Post-trial Obligations

Objectives:

- Appreciate ethical challenges with conducting international collaborative research in low- and middle-income countries
- Understand ethical considerations for defining an appropriate standard of care in clinical trials in international collaborative research
- Understand the obligations investigators and sponsors have to research participants after the conduct of a trial (e.g. post-trial access to any proven effective treatments)

Time	Topic	Faculty
8:30-9:15	Introduction and Standards of Care	Annette Rid, MD PhD NIH Clinical Center Department of Bioethics and NIAID
9:15-9:25	Discussion	
9:25-10:10	Post-trial Obligations	Joseph Millum, PhD NIH Clinical Center Department of Bioethics & Fogarty International Center
10:10-10:20	Discussion	
10:20-10:35	Break	
10:35-11:10	Case Discussion: Placebo-Controlled Trial of Antimalarial Drug	Joseph Millum
11:10-11:30	Perspectives from Kenya	Joseph Millum *in Conversation* with: Dorcas Kamuya, PhD, MPH Head of Health Systems and Research Ethics KEMRI-Wellcome Trust Research Programme Nairobi, Kenya

Reading Assignment

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

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
- Guideline 6. Caring for participants' health needs

Millum, Joseph. Post-Trial Access to Antiretrovirals: Who Owes What to Whom? *Bioethics* 2011; 25(3): 145-154.

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.

Optional:

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