Ethical and Regulatory Aspects of Clinical Research

September 21 to November 9, 2022
8:30-11:30 am
All material to be delivered by NIH Videocast and CANVAS

8.2.22

Overview

Session	Date	Topics	Faculty
1	9/21/22	Introduction/Framework/History/Institutional Review Boards	Taylor, Grady, *Lederer*
2	9/28/22	Study Design/Risk-Benefit/Perspectives from the Field	Taylor, Wendler, *Ledgerwood*, Arlen
3	10/12/22	Subject Selection/ Recruitment and Retention/Inclusion of Children	Taylor, Wendler, *Shah*
4	10/19/22	Equity and Inclusion	Asada, Taylor, *Langford*
5	10/26/22	Informed Consent/Decision Making/Capacity Assessment	Grady, Kim, Todman, Taylor
6	11/2/22	Incidental Findings/Return of Results/Inclusion of Native Populations	Berkman, Jamal, *Claw*
7	11/9/22	International/Standards of Care/Post-trial Obligations/Community Engagement	Rid, *Millum, Kamuya*

Guest Lecturers (unaffiliated with the NIH) noted in *Italics*

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.
- Describe the purpose, function, and challenges of IRBs
- Identify and apply relevant considerations for assessment of research risks and benefits
- Explore the ethical requirement of fair subject selection and its application
- Identify the critical elements of informed consent and strategies for implementing informed consent for clinical research.
- Appreciate ethical challenges with conducting international collaborative research in low- and middle-income countries.

Session 1: Introduction/Framework/History/Institutional Review Boards September 21
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
- Understand the basis of the role and responsibilities of an Institutional Review Board

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	
9:40-10:25	History of Research Ethics	Susan E. Lederer, Ph.D. Robert Turell Professor of History of Medicine and Bioethics Chair, Department of Medical History and Bioethics University of Wisconsin School of Medicine and Public Health
10:25-10:35	Discussion	
10:35-10:50	Break	
10:50-11:20	Institutional Review Boards	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics
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)

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

Journal Articles

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

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

US Federal Regulations

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

Jones DS, Grady C, Lederer S. **"**Ethics and Clinical Research" — The 50th Anniversary of Beecher's Bombshell**.** *New England Journal of Medicine* 2016; 374(24): 2393-2398.

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

Session 2: Study Design/Risk-Benefit/Perspectives from the Field September 28

- Identify ethical issues in the design and conduct of clinical trials
- Identify and apply relevant considerations for assessment of research risks and benefits
- Consider unique ethical issues related to the design and conduct of Phase I trials.

Time	**Topic**	**Faculty**
8:30-9:00	Study Design	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics
9:00-9:10	Discussion	
9:10-9:55	Risk/Benefit	David Wendler, PhD NIH Clinical Center Department of Bioethics
9:55-10:05	Discussion	
10:05-10:20	Break	
10:20-11:20	Phase I Research Roundtable	Julie Ledgerwood, DO *Most recently* Chief Medical Officer and Deputy Director Vaccine Research Center National Institutes of Allergy and Infectious Disease, NIH *Currently* Chief Medical Officer Vaccine Company, Inc.

		Philip M. Arlen, MD Medical Affairs Director – IRB Chair NIH Clinical Research Directorate Frederick National Laboratory for Cancer Research Leidos Biomedical Research, Inc.
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; Chapters 20-21 pp. 144-149)

Part VIII: The Behavior of Clinical Investigators: Conflicts of Interest (Chapter 74; pp. 378-381)

Archived Lecture
https://videocast.nih.gov/watch=42671 (first 60 minutes)

Randomized Clinical Trials: Clinical Equipoise (September 29, 2021)
Robert Truog, MD
Director, Harvard Center for Bioethics
Frances Glessner Lee Professor of Legal Medicine, Professor of Anaesthesia (Pediatrics) Harvard Medical School

Articles

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

Web Resources (for those less familiar with drug/vaccine development process)

Food and Drug Administration. Drug Development Process.
https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

Coronavirus Resource Center, Johns Hopkins University. Vaccine Research and Development.
https://coronavirus.jhu.edu/vaccines/timeline

YOM KIPPUR October 5 – No class

Session 3: Subject Selection/ Recruitment and Retention/Inclusion of Children– October 12

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 children

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	
9:20-10:00	Recruitment and Retention	Dave Wendler, PhD NIH Clinical Center Department of Bioethics
10:10-10:20	Discussion	
10:20-10:35	Break	
10:35-11:20	Ethical Inclusion of Children in Research	Seema Shah, JD Founders' Board Professor of Medical Ethics Associate Professor of Pediatrics Feinberg School of Medicine Northwestern University
11:20-11:30	Discussion	

Reading Assignment

Textbook

Part IV: The Ethics of Research Participant Recruitment (Chapter 22; pp. 155-161, Chapter 27; pp. 179-183, Chapter 29; pp. 185-188)

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

Journal Article

Shah SK, When to start paediatric testing of the adult HIV cure research agenda? *Journal of Medical Ethics* 2017 43: 82-86.

Session 4: Equity and Inclusion – October 19

Objectives:

- Identity the difference between inequality and inequity
- Review Federal Policy intended to diversify those enrolled in clinical research
- Explore the practical implications of diversifying enrollment in clinical research

Time	Topic	Faculty
8:30-9:15	When are Health Inequalities Unfair?	Yukiko Asada NIH Clinical Center Department of Bioethics
9:15-9:25	Discussion	
9:25-9:45	Federal Inclusion Policy	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics
9:45-10:00	Break	
10:00-10:50	What does Commitment to Diversity in Clinical Research Look Like in practice: Protocol Design, Patient, and Staffing Considerations	Aisha Langford, PhD MPH Department of Population Health Co-Director, CTSI Recruitment and Retention Core NYU Grossman School of Medicine
10:50-11:00	Discussion	
11:00-11:30	Case: What does genetics have to say about diversity?	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics

Reading Assignment

Textbook

Part IV: The Ethics of Research Participant Recruitment (Chapters 24-25; pp. 166-175)

Journal Articles

J Jull, M Whitehead, M Petticrew, E Kristjansson, D Gough, J Petkovic, J Volmink, C Weijer, M Taljaard, S Edwards, L Mbuagbaw, R Cookson, J McGowan, A Lyddiatt, Y Boyer, L G Cuervo, R Armstrong, H White, M Yoganathan, T Pantoja, B Shea, K Pottie, O Norheim, S Baird, B Robberstad, H Sommerfelt, Y Asada, G Wells, P Tugwell, V Welch. When is a randomised controlled trial health equity relevant? Development and validation of a conceptual framework. *BMJ Open*. 2017; 7(9):e015815.

R Cookson, M Robson, I Skarda, T Doran. Equity-informative methods of health services research. *Journal of Health Organization and Management* 2021; 35(6): 665-681.

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

Scott E, McComb B, Trachtman H, Mannon L, Rosenfeld P, Thornton R, Bougrab N, Sherman S, Langford A. Knowledge and use of recruitment support tools among study coordinators at an academic medical center: The Novel Approaches to Recruitment Planning Study. *Contemporary Clinical Trials Communications* 2019. 15: 100424.

NIH Inclusion Policies

NIH Guidelines on The Inclusion of Women and Minorities as Subjects In Clinical Research
https://grants.nih.gov/grants/guide/notice-files/not94-100.html

NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects
https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html

Optional

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

Session 5: Informed Consent/Decision Making/Capacity Assessment October 26

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	

10:35-11:00	Capacity Assessment in Practice	Katherine Todman MSW, LCSW-C Human Subjects Protection Unit National Institute of Mental Health
11:00-11:10	Discussion	
11:10-11:30	Nuts and Bolts of Consent	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics

Reading Assignment
Textbook

Part V: Informed Consent in Research (Overview and Chapters 30-32; pp. 189-207; Chapters 36-37; pp. 216-223)

Journal Articles

Grady C. Enduring and Emerging Challenges of Informed Consent, *New England Journal of Medicine* 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 Clinical Center Policy

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

Session 6: Incidental Findings/Return of Results/Inclusion of Native Populations November 2

- 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 and Secondary Findings	Ben Berkman, JD MPH NIH Clinical Center Department of Bioethics and NHGRI
9:15-9:25	Discussion	

9:25-10:10	Returning Research Results in the Context of Evolving Science	Leila Jamal, PhD ScM, CGC NIH Clinical Center Department of Bioethics and NCI
10:10-10:20	Discussion	
10:20-10:35	Break	
10:35-11:20	Genetics and Inclusion of Indigenous Populations	Katrina Claw, PhD Assistant Professor Medicine and Bioinformatics University of Colorado Denver Anschutz Medical Campus
11:20-11:30	Discussion	

Reading Assignment

President's Commission

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

Journal Articles

Schupmann W, Miner SA, Sullivan HK, Glover JR, Hall JE, Schurman SH, Berkman BE. Exploring the motivations of research participants who chose not to learn medically actionable secondary genetic findings about themselves. *Genetics in Medicine* 2021;23(12):2281-2288.

Bombard Y, Brothers KB, Fitzgerald-Butt S, Garrison NA, Jamal L, James CA, Jarvik GP, McCormick JB, Nelson TN, Ormond KE, Rehm HL, Richer J, Souzeau E, Vassy JL, Wagner JK, Levy HP. The Responsibility to Recontact Research Participants after Reinterpretation of Genetic and Genomic Research Results. *American Journal of Human Genetics* 2019;104(4):578-595.

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; 9:1-6.

Optional

Wagner JK, Colwell C, Claw KG, Stone AC, Bolnick DA, Hawks J, Brothers KB, Garrison NA. Fostering Responsible Research on Ancient DNA *American Journal of Human Genetics* 2020; 107(2):183-195.

Saunkeah B, Beans JA, Peercy MT, Hiratsuka VY, Spicer P. (2021) Extending Research Protections to Tribal Communities (Target Article) *The American Journal of Bioethics*2021; 21(10): 5-12.

Krystal S. Tsosie, Katrina G. Claw & Nanibaa' A. Garrison. Considering "Respect for Sovereignty" Beyond the Belmont Report and the Common Rule: Ethical and Legal Implications for American Indian and Alaska Native Peoples (Peer Commentary) *The American Journal of Bioethics* 2021; 21(10): 27-30.

Session 7: International/Standards of Care/Post-trial Obligations/Community Engagement - November 9

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)
- Consider and identify challenges related to community engagement in the design and implementation of research

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 Senior Lecturer Department of Philosophy St. Andrews University Scotland, UK
10:10-10:20	Discussion	
10:20-10:35	Break	
10:35-11:20	Community Engagement in Health Research: Why it Matters and Different Approaches	Dorcas Kamuya, PhD, MPH Head of Health Systems and Research Ethics KEMRI-Wellcome Trust Research Programme Nairobi, Kenya
11:20-11:30	Discussion	

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

Barsdorf N, Maman S, Kass N, Slack C. "Access to treatment in HIV prevention trials: perspectives from a South African community." *Developing World Bioethics* 2010; 10(2): 78-87.

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.

Marsh VM, Kamuya DK, Parker MJ, Molyneux CS. Working with Concepts: The Role of Community in International Collaborative Biomedical Research. *Public Health Ethics* 2011;4(1):26-39.

Optional:

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

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.

Nuffield Council on Bioethics Workgroup. Workshop report: global expert group highlights need for better community engagement during global health emergencies. 2019.