Ethical and Regulatory Aspects of Clinical Research

September 25 to November 6, 2024
8:30-11:30 am
All material to be delivered by NIH Videocast and CANVAS
9.18.24 - FINAL
SYLLABUS

Session	Date	Topics	Faculty
1	9/25/24	Introduction/Framework/History/Institutional Review Boards	Taylor, Grady, *Lederer*
2	10/2/24	Informed Consent/Decision Making/Capacity Assessment	Grady, Kim, Squires (NIMH), Taylor
3	10/9/24	Study Design/Risk-Benefit/Social Value/Inclusion of Children in Research	Taylor, Wendler, *Shah*
4	10/16/24	Equity/Subject Selection/Recruitment and Retention	Asada, Taylor, *Langford*
5	10/23/24	Genomic Sequencing, Return of Results from Field, Conducting Genetic Research with Indigenous Communities	Berkman, Sapp (NHGRI), *Claw*
6	10/30/24	Participant Experience	*Fisher*, Clinical Center Research Participants Panel
7	11/6/24	International/Standards of Care/Post-trial Obligations/Community Engagement	Steel, *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 the critical elements of informed consent and strategies for implementing informed consent for clinical research.
- Identify and apply relevant considerations for assessment of research risks and benefits
- Explore the ethical requirement of fair subject selection and its application.
- Identify challenges and opportunities related to genetics research and research with stored samples
- Appreciate the perspective of individuals who have participated in research
- Appreciate ethical challenges with conducting international collaborative research in low- and middle-income countries

Session 1: Introduction/Framework/History/Institutional Review Boards September 25

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, PhD Ronald L. Numbers Professor 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

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)

Journal Articles

Emanuel E, Wendler D, & Grady C. An Ethical Framework for Biomedical Research. Chapter 11 in The Oxford Textbook of Clinical Research Ethics. Edited by EJ Emanuel, C Grady, RA Crouch, RK Lie, FG Miller and D Wendler (Oxford University Press: New York): 123-135.

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

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.

Core Research Ethics Codes

Nuremberg Code (1949) as published in the British Medical Journal (1996) 313:1448 https://www.bmj.com/content/313/7070/1448.1

Declaration of Helsinki (also known as World Medical Association Declaration Of Helsinki – Ethical Principles For Medical Research Involving Human Subjects) (2013) https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research **Belmont Report** (also known as Ethical Principles and Guidelines for the Protection of Human Subjects of Research) (1979) https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html

US Federal Regulations

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

Session 2: Informed Consent/Decision Making/Capacity Assessment October 2

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 to assess capacity

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	Carol Squires, MSSW LCSW 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

Readings

Textbook

Part V: Informed Consent in Research (Overview and Chapters 30-32; pp. 189-210; Chapters 36-37; pp. 216-223)

Journal Article

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

Food and Drug Administration. Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent August 2023.

Book Chapter

Kim SYH. 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 3: Study Design/Risk-Benefit/Inclusion of Children in Research October 9

- Identify ethical issues in the design and conduct of clinical trials
- Identify and apply relevant considerations for assessment of research risks and benefits
- Consider the unique aspects of the inclusion of children in research

Time	Topic	Faculty
8:30-9:00	Introduction to Study Design	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics
9:00-9:10	Discussion	
9:10-10:05	Risk/Benefit/Social Value	David Wendler, PhD NIH Clinical Center Department of Bioethics
10:05-10:15	Discussion	
10:15-10:30	Break	
10:30-11:20	Ethical Inclusion of Children in Research	Seema Shah, JD Founders' Board Professor of Medical Ethics Professor of Pediatrics Feinberg School of Medicine Northwestern University
11:20-11:30	Discussion	

Readings

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)

Journal Articles

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

Rid A. Judging the Social Value of Health-Related Research: Current Debate and Open Questions. *Perspectives in Biological Medicine*. 2020;63(2):293-312.

Mintz K, Jardas E, Shah S, et al. Enrolling Minors in COVID-19 Vaccine Trials. *Pediatrics*. 2021;147(3):1-5.

Diekema DS. Conducting Ethical Research in Pediatrics: A Brief Historical Overview and Review of Pediatric Regulations. *Journal of Pediatrics*. 2006;149(1 Suppl):S3-11.

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

National Institutes of Health. NIH Clinical Research Trials and You. The Basics. https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics

Session 4: Equity/Subject Selection/ Recruitment and Retention– October 16

Objectives:

- Consider what a commitment to equity can mean in the design, implementation and reporting of clinical research
- Explore the ethical requirement of fair subject selection and its application
- Identify ethical issues and strategies in the recruitment and retention of subjects

Time	Topic	Faculty
8:30-9:10	Equity in Clinical Research	Yukiko Asada, PhD NIH Clinical Center Department of Bioethics
9:10-9:20	Discussion	
9:20-10:10	Subject Selection	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics
10:10-10:20	Discussion	
10:20-10:35	Break	

10:35-11:20	Recruitment and Retention	Aisha T. Langford, PhD, MPH, FSBM Associate Professor Department of Family Medicine and Public Health Sciences, Division of Behavioral Sciences Wayne State University School of Medicine
11:20-11:30	Discussion	

Reading Assignment

Textbook

Part IV: The Ethics of Research Participant Recruitment (Chapters 24-25; pp. 166-188)

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 AT, Orellana KT, Buderer N. Correlates of knowledge of clinical trials among U.S. adults: Findings from the 2020 Health Information National Trends Survey. *Contemporary Clinical Trials.* 2022; 114:1-6.

Langford AT. 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.

Dickert N, Grady C. What's the Price of a Research Subject? Approaches to Payment for Research Participation. New England Journal of Medicine 1999. 341 (3):198-203.

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

Session 5: Genomic Sequencing/Return of Results/Inclusion of Native Populations October 23

- 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	An Overview of Research on Genomic Sequencing and Related Ethical Issues	Ben Berkman, JD MPH National Human Genome Research Institute
9:15-9:25	Discussion	
9:25-10:10	Outcomes Associated with Opportunistic Screening for Secondary Findings	Julie Sapp, ScM, CGC Precision Genomics Section Genomics Services Research Program National Human Genome Research Institute
10:10-10:20	Discussion	
10:20-10:35	Break	
10:35-11:20	Genetics and Inclusion of Indigenous Populations	Katrina Claw, PhD Associate Professor Department of Biomedical Informatics Colorado Center for Personalized Medicine University of Colorado 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

Wolf SM, Green RC. Return of Results in Genomic Research Using Large-Scale or Whole Genome Sequencing: Toward a New Normal. *Annual Review of Genomics and Human Genetics* 2023; 24:393-414
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, Dorr CR, Woodahl EL. Implementing community-engaged pharmacogenomics in Indigenous communities. *Nature Communications* 2024 15(920): 1-5.

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.

Tsosie KS, Claw KG, Garrison NA. 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.

Fleskes RE, Bader AC, Tsosie KS, Wagner JK, Claw KG, Garrison NA. Ethical Guidance in Human Paleogenomics: New and Ongoing Perspectives. Annual Review of Genomics and Human Genetics 2022 23:1, 627-652.

Session 6: Participant Experience – October 30

- Understand the ethical considerations when enrolling healthy volunteers into early phase trials
- Consider the ethical concerns when including, excluding potential participants who do not have access to health insurance
- Appreciate the experience of individuals who have participated in research

Time	**Topic**	**Faculty**
8:30-9:20	Healthy Volunteers in Phase I Trials	Jill Fisher, PhD UNC Center for Bioethics Department of Social Medicine University of North Carolina – Chapel Hill
9:20-9:30	Discussion	
9:30-10:00	Case Discussion	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics
10:00-10:10	Break	
10:10-11:30	Participant Panel	

Reading Assignment

Waltz M, Davis AR, Fisher JA. Death and Taxes': Why Financial Compensation for Research Participants is an Economic and Legal Risk. *Journal of Law, Medicine & Ethics* 2023; 51 (2): 413-425.

Walker RL, MacKay D, Waltz M, Lyerly A, Fisher JA (2022) Ethical Criteria for Improved Human Subject Protections in Phase I Healthy Volunteer Trials. *Ethics & Human Research* 2002; 44 (5): 2-21.

Cho HL, Danis M, Grady C. The Ethics of Uninsured Participants Accessing Healthcare in Biomedical Research: A Literature Review. *Clinical Trials* 2018;15(5):509-521

Session 7: International/Standards of Care/Post-trial Obligations/Community Engagement
November 6

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 and opportunities related to community engagement in the design and implementation of research

Time	Topic	Faculty
8:30-9:15	Introduction and Standards of Care	Robert Steel, PhD NIH Clinical Center Department of Bioethics and National Institute of Allergy and Infectious Disease
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, MSc Head of Health Systems and Research Ethics KEMRI-Wellcome Trust Research Programme Associate Professor Nuffield Department of Medicine, Centre for Tropical Medicine, University of Oxford
11:20-11:30	Discussion	

Reading Assignment

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

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.

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.

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.

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.

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