Ethical and Regulatory Aspects of Clinical Research

September 20 to November 1, 2023
8:30-11:30 am
All material to be delivered by NIH Videocast and CANVAS

8.23.23
DRAFT

Overview

Session	Date	Topics	Faculty
1	9/20/23	Introduction/Framework/History/Institutional Review Boards	Taylor, Grady, *Lederer*
2	9/27/23	Informed Consent/Decision Making/Capacity Assessment	Grady, Kim, HSPU, Taylor
3	10/4/2023	Study Design/Risk-Benefit/Social Value/Inclusion of Children in Research	Taylor, Wendler, *Shah*
4	10/11/23	Incidental Findings/Return of Results/Inclusion Indigenous Populations	Berkman, Jamal, *Claw*
5	10/18/23	Equity/Subject Selection/Recruitment and Retention	Asada, Taylor, Wendler
6	10/25/23	International/Standards of Care/Post-trial Obligations/Community Engagement	Rid, *Millum, Kamuya*
7	11/1/23	Wearables/Brain Implants/LLM	*Gross*, Hendriks, *Rahimzedah*

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
- Appreciate ethical challenges with conducting international collaborative research in low- and middle-income countries
- Apply knowledge gained in course to the inclusion of novel technology in the design and implementation of research

Session 1: Introduction/Framework/History/Institutional Review Boards September 20
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. 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 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.

Rollin F, Van Doren V, Alvarez J, Rousselle R, Bussey-Jones J. Antiracist Structural Intervention at the Emory University Institutional Review Board. *Ethics and Human Research* 2023; https://doi.org/10.1002/eahr.500174

Session 2: Informed Consent/Decision Making/Capacity Assessment September 27

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	Julie Britnall, 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. 189-210; 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.

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 4

- 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 Consider the unique aspects of the inclusion of children in research

Time	Topic	Faculty
8:30-9:00	Study Design	Holly Taylor, PhD MPH NIH Clinical Center Department of Bioethics
9:00-9:10	Discussion	
9:10-10:05	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 Associate Professor of Pediatrics Feinberg School of Medicine Northwestern University
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)

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.

Journal Article

Shah SK, When to Start Paediatric Testing of the Adult HIV Cure Research Agenda? *Journal of Medical Ethics* 2017 43: 82-86.

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

Session 4: Incidental Findings/Return of Results/Inclusion of Native Populations October 11

- 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	An Overview of Research on Genomic Sequencing and Related Ethical Issues	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

Shevchenko Y, Bale S. Clinical Versus Research Sequencing. *Cold Spring Harbor Perspectives in Medicine*. 2016 Nov 1;6(11):a025809.

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

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.

Tsosie KS, 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 5: Equity/Subject Selection/ Recruitment and Retention– October 18

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	Dave Wendler, PhD NIH Clinical Center Department of Bioethics
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.

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.

Steel R, Wendler D. Distinguishing Appropriate from Inappropriate Conditions on Research Participation. *Bioethics* 2023;37(2):135-145.

Session 6: International/Standards of Care/Post-trial Obligations/Community Engagement – October 25

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	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 Nuffield Department of Medicine, Centre for Tropical Medicine, University of Oxford
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.

Session 7: Emerging Tech – November 1

Objectives:

- Apply knowledge gained in course to date to novel topics in research ethics
- Consider the ethical implications of incorporating wearable devices into research design and highlight the promise of blockchain technology and privacy-preserving innovations to facilitate participant ownership of data
- Consider the ethical implications of conducting research with implantable neural devices including: atypical or emerging risks and what responsibilities we have towards participants with implants once the trial is completed
- Consider the ethical, legal and social issues of incorporating Large Language Models (LLMs) to the design, conduct, dissemination, and peer review of research involving humans.

Time	**Topic**	**Faculty**
8:30-9:10	Wearables	Marielle Gross, MD, MBE Assistant Professor University of Pittsburgh School of Medicine Department of Obstetrics, Gynecology and Reproductive Sciences Center for Bioethics and Health Law
9:10-9:20	Discussion	
9:20-10:10	Removal of Brain Implants	Saskia Hendriks, MD, PhD NIH Clinical Center Department of Bioethics
10:10-10:20	Discussion	
10:20-10:35	Break	
10:35-11:20	LLMs	Vasiliki Rahimzedah, PhD Assistant Professor Center for Medical Ethics & Health Policy Baylor College of Medicine
11:20-11:30	Discussion	

Reading Assignment

Tu J, Gao W. Ethical Considerations of Wearable Technologies in Human Research. *Advanced Healthcare Materials* 2021; 10: 2100127.

Hendriks S, Grady C, Ramos KM, et al. Ethical Challenges of Risk, Informed Consent, and Posttrial Responsibilities in Human Research With Neural Devices: A Review. *JAMA Neurolology* 2019;76(12):1506–1514. doi:10.1001/jamaneurol.2019.3523

Bender EM, Gebru T, McMillan-Major A, Shmitchell S. (2021). On the Dangers of Stochastic Parrots: Can Language Models be too Big? In Proceedings of the ACM conference on fairness, accountability, and transparency (pp. 610-623).

Optional:

Gross MS, Miller RC. Ethical Implementation of the Learning Healthcare System with Blockchain Technology. *Blockchain in Healthcare Today* 2019; 22:1-9

Pournaras E. (2023) Science in the Era of ChatGPT, Large Language Models and Generative AI: Challenges for Research Ethics and How to Respond. Preprint submitted to arXiv:2305.15299v4 (July 2023).