2021 OHRP EXPLORATORY WORKSHOP

Review of Third-Party Research Risk: Is There a Role for IRBs?

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OASH Office for Human Research Protections

Summary Report

INTRODUCTION

BACKGROUND

The rapidly changing landscape of biomedical and health-related behavioral research continues to present diverse challenges for adequately reviewing and appropriately regulating research to best protect human research subjects. Charged with the mission of providing leadership in the protection of the rights, welfare, and wellbeing of human subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS), the Office for Human Research Protections (OHRP) endeavors to keep abreast of these challenges with the long-term goal of developing meaningful policy guidance that responds to them. OHRP's Division of Education and Development (DED) promotes education and outreach on the protection of human subjects in research. DED created the OHRP Exploratory Workshop to provide a platform for collegial intellectual exchanges within the research community to promote exploration of topics of interest that hinges on the Federal regulations for human subjects protection.

The conduct of research can have an impact on people who are third parties and who do not meet the definition of human subjects in the Common Rule. This OHRP Exploratory Workshop explores research risks that may impact these third parties.

OBJECTIVES

The purpose of OHRP's Exploratory Workshop is to provide a platform for open dialogue and exchange of ideas between stakeholders in the regulated community. This workshop on third-party research risks will:

- Identify third parties impacted by research and consider what types of risks they might face in a variety of studies;
- Consider whether researchers and the research community have a responsibility, moral or otherwise, to protect third parties and, if so, in what capacity;
- Review real-world examples for potential protections against research risks to third parties; and
- Reflect on the role of institutional review boards (IRBs) for protecting third parties.

AGENDA

Time	Sessions
9:45 AM – 10:00 AM	**OHRP Welcome**
10:00 AM – 12:35 PM	**Session I: What Do We Mean by Third Parties in Research? What Rights and Protections, if Any, Might They Merit?** The research community has generally focused on the protection of human research subjects as defined by the Common Rule. However, sometimes the conduct of research can have an impact on people who are third parties and who do not meet the definition of human subjects. This session will explore who some of the impacted parties are and what types of risks they might face in various types of research. It will not include those third parties whose risks arise from the knowledge gained through the research. Panelists will consider whether researchers and the research community have a responsibility to protect third parties and if so, in what capacity.
10:00 AM	**Session I Overview and Introduction of Speakers** **Moderator:** Nir Eyal, PhD; *Henry Rutgers Professor of Bioethics, Director of the Center for Population–Level Bioethics (CPLB), Department of Health Behavior, Society and Policy, Rutgers University*
10:05 AM	**Who Are Third Parties Impacted by Research?** **a. Research Studies That Do Not Directly Involve Human Subjects** Daniel Nelson; *Emeritus Director, Human Research Protocol Office, U.S. Environmental Protection Agency, Emeritus Professor of Social Medicine and Pediatrics, University of North Carolina at Chapel Hill* **b. Third-Party Risk in Clinical Research Trials** Donn Colby, MD, MPH; *Research Physician, US Military HIV Research Program (MHRP)* **c. Ensuring Privacy, Building Trust: Collecting, Processing, and Sharing Third-Party Information in Social and Behavioral Health Research** David W. Lounsbury, PhD; *Associate Professor, Epidemiology & Population Health, Division of Health Behavior Research and Implementation Science, Albert Einstein College of Medicine*
10:50 AM	**Ethical Considerations for Third-Party Risk in Research** Seema K. Shah, JD; *Founder's Board Professor of Medical Ethics, Associate Professor of Pediatrics, Lurie Children's Hospital & Northwestern University*
11:05 AM	**Limiting Non-Consenting Third Parties to Reasonable Research Risks** Holly Fernandez Lynch, JD, MBe; *John Russel Dickson, MO Presidential Assistant Professor of Medical Ethics, Department of Medical Ethics and Health Policy, Perelman School of Medicine (PSOM), University of Pennsylvania, Founder and Chair, The Consortium to Advance Effective Research Ethics Oversight (www.AEREO.org)*
11:20 AM	**Public Risk Perception and the Creation of Clear Communications** Tamar Krishnamurti, PhD; *Assistant Professor of Medicine and Clinical & Translational Science, Division of General Internal Medicine, University of Pittsburgh*
11:35 AM	**Session I Panel Discussion** Third parties are not directly involved in the research, but they may still incur risk of harm. What are these risks and how may the public or third parties perceive them? Does the research community have a responsibility to protect third parties from potential harms? Are there relevant moral or legal theories that support a charge to protect third parties in research?

AGENDA

Time	Sessions
12:35 PM – 1:30 PM	**Lunch**
1:30 PM – 4:00 PM	**Session II: Do IRBs Have a Role in the Review of Third-Party Research Risks and if so, When?** Currently, there are no regulatory requirements to protect third parties and there is not an accepted structure to support a collective effort to do so. This session will explore the idea of expanding protections to cover third parties in some circumstances. Panelists will discuss whether and what support for this idea already exists in the field of research ethics and whether institutional review boards (IRBs) have a role to play in the oversight of such protections should they be warranted.
1:30 PM	**Session II Overview and Introduction of Speakers** **Moderator:** Leslie E. Wolf, JD, MPH; *Distinguished University Professor and Professor of Law, Georgia State University College of Law and School of Public Health*
1:35 PM	**Do Research Risks to Third Parties Require a Different Conceptual Approach?** Jonathan Herington, PhD; *Assistant Professor of Philosophy, University of Rochester*
1:50 PM	**What if All Ethical Implications of Research Could Be Taken Seriously? Insights and Opportunities from Stakeholder Theory** James Lavery, PhD; *Conrad N. Hilton Chair in Global Health Ethics, Professor, Hubert Department of Global Health, Rollins School of Public Health, Faculty of the Center for Ethics, Emory University*
2:05 PM	**Why (and How) Bystander Protections Make for Good Ethics and Policy** Jonathan Kimmelman, PhD; *James McGill Professor of Medical Ethics, McGill University*
2:20 PM	**Reviewing Third-Party Risks: A Proposed Framework for IRBs (and Researchers)** David B. Resnik, JD, PhD; *Bioethicist and Senior Ethics Specialist, Adjunct Professor of Philosophy and Religion, North Carolina State University, National Institute of Environmental Health Sciences, National Institutes of Health*
2:35 PM	**Are IRBs the Right Oversight Bodies for Protecting Third Parties?** Daniel M. Hausman, PhD; *Research Professor, Center for Population-Level Bioethics, Rutgers University*
2:50 PM	**Session II Panel Discussion** There are many types of research that can pose risk to third parties, including non-human subjects research that typically does not fall under the oversight of IRBs. If the research community has a responsibility towards protecting third parties in research, who should be involved? Would IRBs have a part to play in this effort and if so, how? Should IRBs review and consider protections for third parties? What might be their limitations and how should these be dealt with?
3:55 PM	**Closing**

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OHRP Exploratory Workshop: September 24, 2021

Welcome and Introduction

- Jerry Menikoff, M.D., J.D.; Director, Office for Human Research Protections (OHRP)
- Yvonne Lau, MBBS, MBHL, Ph.D.; Director, Division of Education and Development (DED), OHRP

Dr. Menikoff welcomed everyone to the fourth annual exploratory workshop sponsored by OHRP's DED. The goal of the series is to provide an open forum for stakeholders in the research community to build relationships and discuss important topics related to the Common Rule (45 CFR 46). The Director thanked DED staff for steering, organizing, and conducting this work.

Historically, the research community has focused on protecting subjects of research as defined by the Common Rule. However, third parties who do not meet the definition of subjects and are not directly involved in the research might face the risk of harm. The role of the research community in protecting them is not clear.

Third-party issues can arise in surprising ways. For example, when organs in the body of a deceased person are manipulated for research purposes, other organs may be affected that will be transplanted to third parties who did not consent to the research. How are the interests of the transplant recipients to be protected? The purpose of the workshop is to identify such impacts and explore the role of Institutional Review Boards (IRBs) in addressing them. Dr. Menikoff thanked the speakers, the moderators, and the audience.

Dr. Lau, Director of the DED, also welcomed everyone to the workshop. She noted that according to the Common Rule, a human subject is, "a living individual about whom an investigator (whether professional or student) conducting research:

- Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens."

This session will explore third parties who do not meet this definition. However, it will not address third parties whose risks arise from the knowledge gained from the research.

Dr. Lau welcomed the "exciting" panel of presenters and invited all of them to engage in the discussion following each of the workshop's two sessions.

Session I: What do we Mean by Third Parties in Research? What Rights and Protections, if any, might they Merit?

Session I Overview

- *Moderator:* Nir Eyal, Ph.D.; Henry Rutgers Professor of Bioethics, Director of the Center for Population-Level Bioethics (CPLB), Rutgers University

Dr. Eyal noted that this intriguing topic explores relationships that researchers have not only with research participants, but also with many other parties that might be affected by research. For example, participants in studies of infections could infect their contacts or people working in labs. How do we think about the rights of the latter? Genetic studies are another example; information gleaned by researchers not only includes data about the participant, but also reveals information about that person's relatives. Tests of nuclear weapons have exposed nearly 125,000 residents in French Polynesia to excessive radiation, none of whom were research subjects or gave their consent. Failure to take into account the rights of third parties, also called bystanders, may be unethical and may affect public trust in the research enterprise.

Are such nonparticipants entitled to the same level of protection as subjects? Some people, the moderator noted, might argue that nonparticipants are entitled to even *more* protection. Where is the line? This workshop offers an opportunity to explore these issues within applicable ethical and legal frameworks.

Who are Third Parties Impacted by Research? Research Studies that do not Directly Involve Human Subjects (and Other Square Pegs in Round Holes)

- Daniel K. Nelson, Emeritus Director, Human Research Protocol Office, U.S. Environmental Protection Agency (EPA), Emeritus Professor of Social Medicine and Pediatrics, University of North Carolina at Chapel Hill

Prof. Nelson noted that human subjects research (HSR) is defined and guided by regulations that restrict the applicability of the regulations and tend to focus on risks to immediate participants. This leads to scenarios that are not defined as HSR, but may still impact humans who are not subjects. Even when research is identified and reviewed as HSR, the research may affect persons other than the identified subjects. This creates many scenarios that might be regarded as "square pegs in round holes," with studies or categories of participants that do not fit neatly into the current framework of protections.

The speaker's objective was to provide a broad introduction to the topic of third-party research risk by presenting as many examples as time permitted. He explained that most examples come from the U.S. EPA, the University of North Carolina at Chapel Hill, or from the deliberations on the subject by the Secretary's Advisory Committee on Human Subjects Protection (SACHRP), with some additional examples that became the focus of national attention and

discussion. Some details were omitted or modified for the sake of time.

Examples from non-HSR. Prof. Nelson began by presenting several examples that would not ordinarily be considered HSR. Each case included a brief vignette, followed by identification of the potential third party who might be impacted by the research in some way.

1. In order to study potential occupational exposure of farmers, environmental scientists plan to install air monitors on diesel tractors and sample during times of crop planting and harvesting. There will be no information collected about the farmers themselves, and they will not be asked to deviate from their normal routines. If we accept that the real subject of interest is the tractor and the air around the tractor, there are no human subjects, but there is still a human involved in the process.
   3rd Party: Tractor driver?

2. The next case involved a variation of that same theme. In order to study air quality, inner city students will be recruited to carry small air monitors in their backpacks. There will be no information collected about the students themselves, and they will not be instructed to walk designated routes on their way to and from school or otherwise change their daily routines. The monitors will, however, track their location through Global Positioning System (GPS) coordinates. Is that alone enough information to make them human subjects? Either way, are we concerned?
   3rd Party: Backpack wearers?

3. For a study on air quality in a community, researchers want to place samplers in people's homes. They will place sampling devices in the yard or enter the home and place them outside windows. Researchers will have the homeowner's name and address, but they won't be collecting any survey information from or about the family. The house is the identified subject, but the information collected may be relevant to the homeowner or family.
   3rd Party: Homeowners and families?

4. Citizen scientists are concerned about household lead exposure in lower socio-economic neighborhoods. As a first step, they want to interview homeowners. Questions will focus on the age of the house in which they live, whether there was paint or wallpaper when they moved in, and whether the house had central air conditioning. There will not be any questions about the individuals living in the house. Again, the apparent subject is the house, but the information obtained may have relevance for homeowners and families. In addition, there are frequently questions about citizen science projects: are the citizen scientists subjects themselves, extensions of the research team, or some of both?
   3rd Party: Homeowners? Citizen scientists?

5. A professor in public policy wants to understand how IRBs function and how they approach review of certain projects. She conducts key informant interviews with IRB directors. She collects information about IRB workload, turnaround time, and institutional policies, but nothing about the individuals themselves. The respondents

might be seen simply as conduits of information, not subjects. Nevertheless, people might be adversely affected by the results of the study. Prof. Nelson observed that issues related to third parties often arise in key informant interviews in a variety of organizational contexts, where the "unit of interest" is the organization, its policies, or outcomes, and not the person providing information.
3rd Party: IRB directors, members, or staff?

6. Students want to test their hypothesis that pharmacists discriminate against people on the basis of race and general outward appearance. They propose to present themselves (in various combinations of dress, cleanliness, and ethnic background) using a standardized script that asks for help from the pharmacist on duty. If this is to be considered as research, there is some deception involved, but it is not clear there are human subjects. One reviewer noted that many pharmacies have an emergency call button under the counter to summon police. Could the student-researchers arouse suspicion and potentially put themselves at risk?
   3rd Party: Pharmacists, students posing as fake patients?

7. In order to assess response(s) by management, a professor of organizational behavior sends letters to 200 top restaurants in a major city, claiming that a diner contracted severe food poisoning after a recent visit to celebrate an anniversary. There are people whose jobs may be at risk from this false information, including the researcher himself (whose dean was not very happy about repercussions from the study).
   3rd Party: Restaurant manager, chef, waitstaff, vendors… and researcher?

HSR studies that may still pose third-party risks. Prof. Nelson provided an additional group of examples that would be reviewed as HSR but might affect third parties who are not considered subjects.

1. A university is awarded a grant to implement a novel method for recycling graywater. Selected dorm rooms will be outfitted with specialized plumbing to supply showers and toilets with graywater. Students living in these rooms will be enrolled with consent, compensated for room and board, and instructed not to use the graywater for drinking or toothbrushing. This consent and cautionary instruction would not, however, extend to unknown others who might pass by or visit the affected rooms.
   3rd Party: Friends, visitors, other dorm residents?

2. Researchers want to study mobility and interactions among the elderly with dementia by placing wide-angle video cameras in the public area (e.g., dining room) of assisted living facilities. The researchers will not know the identities of individual residents and will destroy the videos after analyzing movements using pseudonyms for the residents. This "all-or-nothing" study is to be conducted under a waiver of consent. Families will be notified.
   3rd Party: Passers-by, visitors, facility staff?

3. Infectious disease experts are working to improve treatment of gonorrhea by manipulating the bacterial coat, infecting subjects in a controlled manner, and then

testing for antimicrobial efficacy.
3rd Party: Current or future sexual partners?

4. A participant in a genetic pedigree study is revealed to have been adopted at birth, having grown up believing that her adoptive parents were her birth parents. (This scenario has become increasingly common as genetic testing expanded.)
   3rd Party: Adoptive parents, birth parents, siblings?

5. Genetic specimens are obtained from a representative sample of an isolated population with only a few hundred members. Results of secondary studies (repurposed samples) are potentially stigmatizing for the group at large. (This scenario was drawn from the case involving the Havasupai Tribe in Arizona.)
   3rd Party: Community members beyond immediate participants.

6. In-home interviews for a study on the spread of human immunodeficiency virus (HIV) in poor, rural communities include questions about sexual promiscuity and domestic violence.
   3rd Party: Domestic partners, personal safety research assistants conducting interviews.

7. An interventional study for morning sickness includes diet modification by the expectant mother.
   3rd Party: The developing fetus (the one third party specifically recognized by federal regulations, in Subpart B of 45 CFR 46).

8. An interventional study for post-partum depression involves medication that may end up in breast milk.
   3rd Party: Nursing infant.

9. A survey of adult twins collects information about family members, including potentially sensitive details about their parent's physical characteristics and mental health. Prof. Nelson noted that collecting family history is a standard element in many studies, but parental objections in this study prompted a national discussion of third-party research risks.
   3rd Party: Family members (unconsented).

Who are Third Parties Impacted by Research? Third-Party Risk in Clinical Research Trials

- Donn Colby, M.D., MPH; Research Physician, U.S. Military HIV Research Program (MHRP)

Dr. Colby focused his remarks on clinical trials involving infectious diseases, especially the challenges posed in research seeking a cure for HIV/AIDS. He noted that there are four strategies that have been used in clinical trials intended to better understand infectious diseases that could potentially cause third-party risks:

- *Withholding effective treatment*. The infamous Tuskegee Institute Syphilis Study was an example of this. This approach is not acceptable.

- *Providing treatment that might not be effective.* New antimicrobial drug studies are an example of this approach, which is used routinely.

- *Intentional exposure.* This approach is also used but not routinely. COVID challenge studies are one example. In a study underway in the United Kingdom, up to 90 volunteers – the healthiest people the researchers can find – are being exposed to the virus under carefully controlled conditions.

- *Withdrawing effective treatment.* This is the approach used in research seeking a cure for HIV/AIDS, and the remainder of Dr. Colby's remarks focus on this strategy.

Analytic Treatment Interruption. Dr. Colby reminded us that HIV/AIDS was once an incurable disease, and everyone who had it died within 5 to 10 years of infection. Today, it is treated with antiretroviral therapy (ART); one pill a day controls symptoms, keeps the disease from progressing, prevents suppression of the immune system, allows people to have a normal lifespan, and keeps them from transmitting the disease to others. Effectiveness is easily measured with a blood viral load test. However, long-term risks are still unknown, and strict adherence to the prescribed regime is essential to prevent drug resistance. Also, treatment is very costly (approximately one million dollars for lifetime treatment). Current clinical trials are aimed at removing the need to take drugs to control the disease.

How do we know that a new treatment is effective if the current treatment is already highly effective? There is no blood test yet for HIV/AIDS cure or remission. The only current way to evaluate new treatment for efficacy is called Analytic Treatment Interruption (ATI). Researchers stop ART so that they can evaluate the effects of the new treatment.

Stopping ART for study purposes is done in in a closely-monitored medical setting with

frequent evaluation of clinical, immunological, and virological parameters. It is usually implemented in the context of a clinical trial designed to evaluate the efficacy of the intervention. Researchers seek to protect participant safety by restarting ART *before* clinical symptoms or immunodeficiency occur. The "pros" of this approach are that it is safe for participants, acceptable to people living with HIV/AIDS (PLWH), and acceptable to IRBs. "Cons" include the potential for symptoms if the HIV viral load rebounds quickly, with the possibility that HIV will be transmitted to others through sexual contact or exposure to blood. Unfortunately, this has occurred, but known instances are rare.

Mitigating risks of stopping ART. Research conducted at the Thai Red Cross AIDS Research Centre has sought to address the risk to third parties through the use of the following strategies:

1. **Pre-Screening.** The study excludes potential participants who exhibit risky sexual behavior or are likely to be nonadherent to study procedures.

2. **Informed consent.** Researchers inform potential study participants about the risk for viral rebound and HIV transmission and advise them to use barrier protection during ATI for both contraception and HIV prevention. They also offer counseling to sexual partners and, if indicated, refer them to receive pre-exposure prophylaxis (PrEP*),* which is medicine that people at risk for HIV take to prevent their acquiring HIV from sex or injection drug use.

3. **Monitoring and counseling.** While the study participant is off ART, clinicians frequently assess the person's clinical status and screen for viral rebound. They also discuss the person's risk behavior and offer HIV prevention counseling at every visit.

In interviews, subjects express concern about the risk for transmission, but they also want to "feel normal" and help make progress in research, liberating others. Therefore, they are willing to participate even if there is some risk.

Dr. Colby closed by reviewing a number of ways to mitigate third-party risk in ATI trials:

- Work with Community Advisory Boards to get input from the PLWHs and their partners.
- Screen out potential participants at high risk for sexually transmitted infections (STIs) or non-adherence to study procedures.
- Counsel participants carefully during informed consent and at every visit.
- Offer counseling, HIV testing, and PrEP (or referral to PrEP) to sexual partners.
- Conduct frequent STI screening.
- Consider restarting ART if there is evidence of risky sexual or drug behavior.

Who are Third Parties Impacted by Research? Ensuring Privacy, Building Trust: Collecting, Processing, and Sharing Third-Party Information in Social and Behavioral Health Research

- David W. Lounsbury, Ph.D.; Associate Professor, Epidemiology & Population Health, Division of Health Behavior Research and Implementation Science, Albert Einstein College of Medicine

Dr. Lounsbury explained that his remarks would focus on privacy risks for primary, secondary, and tertiary parties in social-behavioral research. Such research often uses *social network assessment* (SNA) to obtain information about significant others in the life of a primary research participant. The participant is asked to share information about secondary parties, such as proximal family members (biological or "chosen"), friends, workplace associates, and teammates.

In assessing possible privacy risks, the speaker emphasized, it matters what we ask, of whom we ask it, and where we ask it. While SNA is useful in studying health risk behaviors, the risk increases if the individual's primary and other sexual partners or family members would be identified (Margolis, 2000; Abel et al., 2002). Risk is also elevated if the individual is recruited using the internet and social media (Bender et al., 2017).

Third-party risk is easily managed in some designs. For example:

- "Snowball" sampling consents all who are recruited and can protect the identity of the primary participant and others.
- If participants are asked only about overall activities or tendencies of others, again, no privacy concern exists (Lounsbury et al., 2007).

Risks in specific types of socio-behavioral research. Dr. Lounsbury then described the risks to third-parties in several different types of studies that use SNA and reviewed mitigation strategies to address these risks.

Family-focused research. In such studies, the unit of analysis is the family itself. This is arguably the most common subcategory of SNA. The management of privacy concerns for secondary subjects is the primary concern. After a father objected to a survey in which his daughter intended to participate, privacy concerns were highlighted and "deeper thinking" occurred. New regulations issued for the Health Insurance Portability and Accountability Act (HIPAA) have added protections. Concerns for family members we taken into account in the development of the protocol for a 2003 study, *Family Access to Care Study* (5R01-MH063045), and prompted an article highlighting these concerns (Lounsbury et al., 2007).

Nominational sociometric designs. This approach is effectively deployed in classrooms, workplaces, and other settings to study the effects of peer interactions on health and wellbeing. Studies might ask questions about conflict, decision-making strategies, and lifestyle habits that could be viewed as intrusive. A given participant could be both a primary and secondary

subject, and a peer might identify others who have opted out of the study. Hence, procedures must cover the privacy risk to participants and nonparticipants alike.

Qualitative research. This broad category of research uses a variety of methods, including in-depth interviews, focus groups, observation, self-documentation, and analyses of text-based sources (including social media sources). The risk is that such research may intentionally or unintentionally elicit sensitive and/or identifiable third-party information. The speaker made the following recommendations to mitigate these risks:

- Consent should cover risks and any plans for data sharing and dissemination.
- Remove/redact Protected Health Information (PHI) and consider applying site pseudonyms in public reports.
- Recruit more than one informant per category and study more than one setting.
- Among coders, use coding queries as an alternative to full transcripts.
- Conduct "social audits" of results and conclusions prior to public reporting; check in with participants about how their information is being used.
- If sensitive information is found, petition for non-disclosure of qualitative data.

Internet-based and social media research. This category comprises any research that uses the internet as a vehicle for recruiting or interacting, directly or indirectly with subjects, especially social networking sites (for example, on Facebook or Twitter). It has proliferated rapidly. Many individuals (even investigators) either are unaware of the privacy risks of online activity or consciously accept a trade-off in exchange for their privacy. Such research blurs public and private boundaries of online spaces (Bender et al., 2017). Sensitive data can easily be accessed, shared, hacked, and/or replicated, in comparison to data collected in non-internet-based studies.

Third parties as subjects. When is a third-party a research subject? The speaker suggested that IRBs need to consider two questions. First, is the information collected private? Secondly, if it is, is the third party individually identifiable? Can the identity of the third party be readily ascertained by the investigator? If the answer to both of these questions is yes, then the third party should be considered a research subject.

Can the IRB waive informed consent for third-party research subjects? If the research involves greater than minimal risk to the third-party subject, then a waiver should not be granted. If the research does not pose greater than minimal risk to third parties, a waiver may be indicated when the answer to the following two questions is yes:

- Does obtaining the informed consent of third-party subjects pose potential adverse effects to primary research subjects?
- Is it impracticable to obtain the informed consent of third-party subjects?

In determining the level of risk posed, Dr. Lounsbury stressed that privacy issues derive from social norms. The need for privacy is a function of generally accepted social norms and individual expectations about what information should and should not be shared with others. Protecting research participants' right to privacy requires respect for their autonomy and right

to self-determination, as well as support for their general welfare. Third parties' expectations of privacy and the importance of maintaining trust in researchers are both relevant considerations. In addressing issues related to the privacy rights of third parties, the challenge for IRBs is consider the potential for people to be identified and the level of privacy protection already in place in order to determine whether additional safeguards are necessary.

Investigators must decide how best to inform users about the potential for a privacy breach and the implications if this should occur. They also need to design strategies to protect users from privacy breaches or from inadvertently sharing information about themselves. In general, Dr. Lounsbury suggested, investigators should provide certain information about the planned involvement of secondary and tertiary parties to IRBs. On a protocol-by-protocol basis, IRBs may then judge whether the study includes secondary or third-party subjects, and if so, whether their consent should be obtained.

To assist IRBs in assessing risks to third parties and understanding how they will be mitigated, the speaker encouraged investigators to include each of the following sections in the protocol submitted for review:

1. *Rationale for collection of third-party information*: Note the extent and nature of information to be collected and clear scientific purpose.
2. *Procedure for recruitment of participants and informed consent*: Discuss the potential for selection bias/drop out and the risks posed.
3. *Strategy for data collection:* Burden, sensitivity, identifiability; use of study ID codes.
4. *Technique of processing and storing raw data:* Recording, unlinking and linking devices; monitoring strategies.
5. *Manner of disseminating reported findings:* Share pertinent findings with primary and, when possible, third-parties to foster trust and rapport; describe means of information sharing.

The speaker summarized key points as follows:

- Social and behavioral research involving third-party information requires special consideration.
- Investigators and IRBs each need to be more conscientious about how design of a study may affect the rights and welfare of third parties.
- IRB decisions about the management of third-party information must serve to support personal privacy expectations, which are derived from social norms about information sharing.
- We need broad strategies that serve to promote positive public sentiment about science and trust in researchers, which will generate improved participation and higher scientific yield.

Ethical Considerations for Third-Party Risk in Research

- Seema K. Shah, J.D.; Founder's Board Professor of Medical Ethics and Associate Professor of Pediatrics, Lurie Children's Hospital and Northwestern University

Existing regulations and guidance. Prof. Shah's presentation placed third-party risk in the context of existing regulations and guidance. She also explored why third-party risk matters ethically, whether third parties should be treated in the same way as research participants, and whether there should be an upper limit on third-party risks. Finally, she considered why common and unusual risks might need to be treated differently.

The speaker noted that there is no mention of third-party risk in the Common Rule, with the exception of fetuses and breastfeeding infants (Subpart B). IRBs following the Common Rule are explicitly instructed not to consider long-range risk or the possible implications of the research on policy-making. Some understand this instruction to preclude consideration of risks to third parties, but others see this as a way to distinguish IRB review from policy analysis.

Limited ethical guidance is available. The National Research Council and Institute of Medicine noted, in the context of research on housing-related health hazards, that investigators may have obligations to address third-party risks that are "foreseeable and significant" (2005). Also, the Council for International Organizations of Medical Sciences (CIOMS) advises researchers to consider the aggregate risks of research, including risks to "groups and populations" (2016).

Ethical concerns in research with third parties. Why does third-party risk matter ethically? To answer this question, Prof. Shah focused on the fact that some third parties cannot consent to the research. This means that the functions of consent – to protect autonomy, to protect one's interests, and to ensure transparency, trustworthiness, and control – may not be fulfilled.

Since the lack of notice means that third parties cannot take precautions to protect themselves, the research team could cause harm to them and damage to public trust might ensue. If the risk posed is a common one, people are less likely to be harmed. However, if the risk is unusual, people are unable to take precautions, harm is more likely, and public trust is more likely to be impaired. An example of unusual risk would be a Zika virus challenge study in which some third parties at risk of infection have never travelled to a country where the virus is a serious risk, would not usually expect to encounter it, and would not know how to protect themselves. (See Prof. Fernandez Lynch's remarks for a fuller discussion of this example.)

Should we treat third parties the way we treat research participants? Prof. Shah noted that there is a central tension in research ethics between exposing individuals to risk and possible societal benefits of the research, a tension that is managed both through consent and limits on risk.

Should we treat third parties the same as or differently than research participants? The speaker stated that there is no good moral distinction between third parties and research participants who don't consent. Harm to third parties may raise equal if not more concern than harm to participants. When possible harms cannot be anticipated by third parties, researchers may appear particularly irresponsible for exposing people to such harms. On the other hand, an

argument for treating third parties differently and potentially permitting a higher level of risk might be that since regulations don't "box us in," it is possible to fix errors in how research participants are treated.

Should there be an upper limit of risk for third parties? The Nuremberg Code (1947) stated that the "degree of risk to be taken should never exceed that determined by the humanitarian importance of the problems to be solved by the experiment." Some modern guidelines prohibit "excessive" or "unreasonable" risks, and IRBs are asked to determine whether "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" (45 CFR 46.111). Risk limits exist in order to protect those who cannot consent, address information asymmetry, acknowledge that benefits from research are uncertain, preserve public trust in research, and to act as a responsible steward of public trust (London, Kimmelman, & Emborg, 2010; London, 2012).

Prof. Shah summarized the key points of her presentation as follows:

- Despite limited attention in regulations and guidance, there are good reasons to address third-party risks.
- We should be especially cautious about third-party risk when it adds new or uncommon risks.
- On balance, it seems appropriate to treat third parties the same as research participants.
- There are reasons to support an upper limit of risk for third parties and participants, including preserving public trust. It is admittedly hard to measure public trust, but the consequences of low public trust are well documented.
- We need to do a better job of studying what can impact public trust in research.

Limiting Non-Consenting Third Parties to Reasonable Research Risk

- Holly Fernandez Lynch, J.D., MBe; John Russell Dickson, MD; Presidential Assistant Professor of Medical Ethics, Perelman School of Medicine, University of Pennsylvania; Founder and Co-Chair, the Consortium to Advance Effective Research Ethics Oversight (www.AEREO.org)

Prof. Fernandez Lynch focused on third parties affected by research but for whom notice or consent is not possible or advisable. Some third parties may not be identifiable in advance or may be incapable of consent (e.g., a fetus or child). Informing them of the research might breach participant privacy or inhibit participant autonomy. In addressing research risk to these third parties, Prof. Fernandez Lynch focused her remarks on the foreseeable risk of *physical* harm as opposed to emotional or other types of social harm. She explored the question:

- What is the scope of the responsibility to protect non-consenting third parties from physical risks stemming from research?

The speaker used a proposed Zika Virus Controlled Human Infection (CHI) Trial as a case study. CHI studies intentionally expose healthy subjects to a pathogen to study pathogenesis

and/or evaluate investigational prevention or treatment interventions. In 2017, NIH consulted an ad hoc work group to help determine whether it should fund a CHI trial to help advance development of a vaccine against Zika virus infection (Shah, Kimmelman, Lyerly, Lynch, McCuthan, Miller et al., 2018). The working group determined that known risks to subjects would be in line with those of a Phase I trial and could be justified with consent and risk minimization (including confinement). However, consultants were concerned about social value, as well as the potential risk to third parties. Concerns included:

- Uncertainty about how long someone would be able to transmit the virus to others;
- Potential exposure of sex partners, fetuses, and community contacts;
- The possibility that third parties would not be able to be informed of, protect themselves from, or consent to these risks.

In Phase I trials and in prior challenge studies involving other pathogens, risks to third parties typically have been reduced to near zero, leading the working group to recommend that risks to third parties from a Zika challenge study also should be near zero. However, that standard could not be met at the time due to uncertainties about viral transmission. The working group also concluded that the social value of the research was not so great as to justify the level of risk the study would present, given that sponsors were not planning to wait for challenge study results. Ultimately, the group recommended that NIH not proceed with Zika virus challenge studies at that time.

Consideration of research analogies. Prof.. Fernandez Lynch pointed out that the "near zero" risk standard recommended by the Zika CHI study working group would actually grant *more* protection for third parties than for research participants who were enrolled under a waiver of consent. More recent recommendations regarding ethical standards for SARS-CoV-2 controlled human infection studies were less stringent regarding risks to third parties: "For SARS-CoV-2 CHIs to be ethically permissible, risks to participants, study personnel, **and third parties** should be minimized, reasonable in relation to the social value of the research, and below the upper limits of acceptable risk**"** (Shah, Miller, Darton, Duenas, Emerson, Fernandez Lynch, et. al, 2020).

How much research risk to third parties is too much? For consenting research subjects**,** there is no upper bound in the regulations. However, a waiver of consent is permitted under the Common Rule only if research poses "no greater than minimal risk," meaning that the risks of the study are on par with those faced in daily life. Prof. Fernandez Lynch argued that third parties need not be offered *greater* protection than research participants for whom consent is waived. This means that a minimal risk standard, rather than "near zero," would be the appropriate limit. However, she then asked whether it could be possible to justify risks any greater than minimal for non-consenting third parties.

Prof. Fernandez Lynch cited several instances in which non-consenting participants can be exposed to risks that are greater than minimal under federal regulations. For example, FDA regulations permit "Exception from Informed Consent" for emergency research. Surrogates are allowed to consent on behalf of subjects who are unable to consent on their own behalf. Fetuses obviously cannot consent to research in which the pregnant parent wishes to participate.

However, Prof. Fernandez Lynch explained that each of these examples was a poor analogy for non-consenting third parties. She concluded that, under relevant research analogies, risks to third parties who do not consent to research should be bounded by the same risk threshold as applied to subjects who do not consent, namely minimal risk.

Tort law analogies. Prof. Fernandez Lynch then moved beyond research analogies to other social contexts in which people are exposed to risk without consent, including the "reasonableness" standard in tort law. Torts involve harms imposed without consent – but such harm is only legally cognizable if the perpetrator behaved unreasonably. The negligence standard requires the breach of duty of reasonable care. If no breach of duty has occurred, then it is allowable under the law to impose risks and burdens on others without their consent and without compensation. Seen through the lens of tort law, the duty is not to limit one's behavior to only a minimal risk of harm, but rather to behave reasonably. The reasonable person must consider:

- Social values of interest to be advanced vs. those impeded.
- The possibility of alternative, less risky approaches.
- The possibility to avoid harm through self-protection or other means.

Prof. Fernandez Lynch concluded that tort law analogies suggest that both third parties and subjects can be exposed to reasonable risk without consent.

Which standard – research analogies or tort law analogies - should apply to research risks imposed without consent? The answer, said the speaker, depends on whether research risks are regarded as "special." The current system assumes they are and provides special oversight for them.

When consent is not feasible, Prof. Fernandez Lynch advised, community consultation can help identify potential harms to third parties and ways to mitigate these risks. Investigators can then determine if remaining risks are reasonable and strive to increase transparency to enable both subjects and third parties to take appropriate precautions.

Public Risk Perception and the Creation of Clear Communications

- Tamar Krishnamurti, Ph.D.; Assistant Professor of Medicine and Clinical and Translational Science, Division of General Internal Medicine, University of Pittsburg

Dr. Krishnamurti focused her remarks on how people make decisions about their health and tools to enhance health. She often works in the space of maternal health, in which fetuses are recognized third parties under federal regulations. Protections for fetuses, however, may pose risks to mothers, and sometimes the level of risk must be inferred without information – as in the recent case of the FDA-approved Pfizer vaccine for COVID-19, which had no data for pregnant people. This illustrates the challenges of prioritizing the risk considerations of any specific group (third or first party) at the cost of another group, without offering clear communication about this decision-making process. When we lack the evidence we need to

make an informed choice, the lack of evidence makes us vulnerable.

Assessing risks. Every day, as the pandemic continues, we are all trying to minimize our vulnerability. The endless decisions can be exhausting. The silver lining is that the experience provides an opportunity to review what we know about third-party decision-making and how we assess risks.

When we make judgements about risk, we seek the best answers we can find to four basic questions:

- What (and to whom) is the risk?
- How bad is the possible outcome?
- How likely is that outcome?
- What is an acceptable choice?

Risk evaluation is not only a cognitive process, but also an emotional one. For example, our decision might be affected by the pain caused by a child's possible hospitalization. Our thinking is limited by our ability to process relevant information – our numeracy and literacy levels in particular. The novelty of the information presented will affect our ability to process it. Also, we've learned that we tend to be more risk averse when making decisions that affect those for whom we feel responsible, such as our children, parents, or patients. Psychological distance also affects the degree of responsibility we feel we have to other people affected by our decision (i.e., social context).

Communicating risks to third parties. Dr. Krishnamurti presented a few key rules for designing clear communications:

1. Analyze the decisions that people face.

2. Characterize peoples' current beliefs, values, and constraints. Understand what people already know and avoid unhelpful repetition. Understand the daily reality of the target audience and be aware of barriers to taking in new information.

3. Draft messages with clear, structured comparison of alternatives. Present the best available actionable knowledge and allow information to stand on its own merit.

4. Evaluate and iterate. Refine messages based on what you learn.

5. Disseminate information responsibly. Use multiple reliable and trusted sources.

Failure to think through how we communicate about risk can have serious consequences. To show how communication can affect behavior and affect third parties, Dr. Krishnamurti cited the example of at-home testing kits for COVID-19 approved by the FDA. Using the example of one such kit approved by the European University Association (EUA), she noted that FDA's authorized instructions left a great deal of ambiguity about how negative results should be interpreted, specifically given the possibility of a false negative. Instructions for negative

and positive results were essentially the same. Researchers sought to offer a clearer set of instructions and tested them with a MTurk sample. In a hypothetical randomized decision-making experiment, science-based instructions for high-risk scenarios resulted in a higher quarantine rate and better protection for third parties.

The speaker stressed the conclusion that the way in which risks are communicated to first parties can have an impact on third parties, and vice versa. The same lessons that apply in designing communications targeting first parties are applicable to third-party decision-making. For example, it is important to design consent forms to include risk information about how subjects' actions may affect third parties. Public risk communications around third-party risks should be carefully considered. Researchers should use good risk communication techniques to elicit public opinions about acceptable third-party risk, to identify public concerns and values related to third-party risks, and to better ensure that such risks are understood and that third parties are protected as well as possible, within reasonable bounds.

Session I Panel Discussion

Dr. Eyal explained that any presenter could ask a question of any other presenter to open the discussion.

Practicability. Prof. Nelson responded to Prof. Fernandez Lynch's presentation. He said he agreed with her that there is no reason that third parties should not receive the same level of protection as research participants. He was concerned, however, about the issue of practicability in the context of waivers of consent. The majority of clinical studies routinely request participants to supply a family history, but if it is necessary to ask the entire family tree to consent, the study may not be possible.

Prof. Fernandez agreed that there are third parties that could or should not be asked for consent, whether because they are unknown or because consent is not practicable. One of the most challenging situations from an ethical standpoint is when at-risk third parties are known, but there is an issue around whether they should be allowed to prevent the potential subject from enrolling in the research.

Ethical responsibility. Dr. Eyal asked whether it is possible to be overprotective of third parties. For example, in the search for a cure for HIV/AIDS, if thresholds for restarting antiretrovirals are too low, this could keep the research from being successful. Dr. Colby said he did not think the current trials are overprotective. Boundaries are pushed now more than they were when the research first started, allowing a bit more risk. Prof. Shah stressed that though the scientific value of the research is important, there is still a limit to what level of third-party risk should be tolerated.

Dr. Kimmelman asked Dr. Colby how third-party risk is being evaluated in the search for an HIV/AIDS cure. Dr. Colby said this is very difficult. Fortunately, HIV/AIDS is much harder to transmit than other infectious diseases. Each participant is carefully counseled and participants are selected for demonstrated adherence to protocols. However, once a participant

is out in the community, researchers have no control over their behavior. This brings up issues related to confidentiality and disclosure, and so far, there is no real answer about how to operationalize a plan to completely eliminate third-party risk. Dr. Kimmelman noted that once the cure is rolled out to the general population, there will be no capacity to select participants. Dr. Colby rejoined that at this point the cure would no longer be in the research stage.

Dr. Eyal asked whether it makes a difference whether the risk to third parties is the result of the researchers' negligence – for example, a failure to guard data – or instead stems from the failure of research subjects themselves to follow instructions. In the latter case, do the researchers have any responsibility? Prof. Fernandez Lynch gave the example of a challenge study in which participants exercise their right to leave the study and are still infectious, extending risk to third parties. She held that researchers are responsible for anticipating and planning for this possibility. Ethics require that investigators take precautions to deal with foreseeable risks.

Dr. Lounsbury agreed that it was critical for researchers to be proactive and to gather information during the consent process about how participants would act in certain scenarios – for example, dropping out of the trial while still infectious. To help ensure that subjects would adhere to guidelines, he emphasized that time spent building rapport between subjects and researchers is time well spent.

Prof. Shah said the researcher and the IRB share the responsibility to build in procedures that minimize the possibility that harms might occur as the result of negligence. However, it matters whether the harm has a high probability of occurring or very little. Harms are not always foreseeable. There is a legal concept of an "intervening cause," which refers to someone who acts in between the first person and the person who is actually harmed. This concept might be applied to help consider the issue of responsibility.

Reasonableness. Dr. Herington liked the idea of the "reasonableness" standard earlier expounded by Dr. Fernandez Lynch and found it helpful. However, he noted that third parties have different capacities to protect themselves from risks. Risks and benefits might be distributed differently for a variety of reasons and this should be taken into account.

Dr. Lavery observed that Dr. Krishnamurti's presentation emphasized the categorization of risks and how they may be assessed by third parties. However, he said, shockingly little is known about the extent to which people's judgements actually reflect the real world. There is no single view of what constitutes risk. Similarly, it is difficult to pin down what public trust really means and measure it. It is important to get "more traction" on the empirical side of these key issues.

Dr. Colby, speaking from the perspective of a researcher who often works overseas, noted that cultural perspectives can change the perception of what kind of risks appear reasonable. Both the IRB and the community may assess them differently from the way the researcher might expect. Prof. Fernandez Lynch agreed, noting that the notion of reasonableness is an amorphous one, fleshed out in law through precedent. Community consultation is very important. Dr. Lounsbury contrasted his experience with genetic research in Nigeria, in which

there is "almost a bias to participate" because of the high level of trust in doctors, to his experience with the same type of research in the Bronx, where people are more resistant to providing information.

Prof. Shah asked Dr. Krishnamurti whether successfully creating risk communication strategies that are more likely to protect third parties depends on the social-cultural context. Dr. Krishnamurti said that acceptable levels of risk may change depending on the environment. In decision-making, people determine their own threshold for risk, and researchers need to hear their voices. Dr. Krishnamurti also noted that in operationalizing the concept of reasonableness, investigators are obligated to strive for transparency of communication. They need to understand people's ideas on what risks are reasonable, taking into account the social determinants of health.

Dr. Hausman observed that surrogates are sometimes used to make decisions for others who cannot consent. Community consultation might be considered a form of surrogate decision-making on behalf of those in community who cannot be consulted directly. Prof. Fernandez Lynch thought this concept did not transfer well to consideration of third parties, since surrogates, unlike community consultations, focus on the interests of specific individuals.

Identifying third parties. Dr. Eyal asked who exactly should be considered to be a third party who deserves forethought and consideration of their rights in research design. For example, in research related to pharmaceutical drugs, do the interests of the Chief Executive Officer (CEO) of the drug company or the company count? He noted that the chance that "something bad will happen to someone out there" is increased by the number of third parties involved. The issue of public trust looms larger.

Dr. Kimmelman said that a CEO is not a third party as defined for our workshop; the individual might be harmed by the *findings* of the research, but not by the research itself. There is also a sense in which the company sponsor has already consented to whatever harms may occur. In terms of other third parties who might suffer harm, he noted that if a goal of the research is to create an environment in which there is a high level of trust in the research enterprise, the population of concern is broader than if consideration is limited to involuntary harms to individuals. He also noted that the notion of who counts as a third party will differ in different cultural contexts. The matter is further complicated by the fact that what happens in one country might well affect people in another country.

Dr. Resnik, who noted that he had written an article on this topic (Resnik & Sharp, 2006), held that consideration of research effects on third parties should be limited to identifiable third parties. Once you begin thinking of groups of people you cannot identify, he said, the process begins to sound more like policy making for the public in general. However, the specific person affected is likely to be unknown. For example, if people are released from care when they are still under the effect of anesthetics, their poor driving might kill someone whose exact identity could not be known.

Prof. Shah disagreed; she held that risks posed through subjects' behavior could not be limited to identifiable third parties. Dr. Colby agreed with her. He cited two cases in which subjects

transmitted HIV/AIDS to regular sexual partners who were known and had already received counseling from the researchers. This occurred despite counseling and the precautions described earlier. However, if transmission is also occurring to casual sexual partners unknown to the researchers, then it is less likely to be recognized and come to the attention of the researchers.

Citing differences between discreet and continuous variables, Dr. Lavery held that "different types of analysis" were needed for "messier" variables. Such issues can be approached through stakeholder theory, which focuses on the interests of categories of individuals.

Dr. Resnik emphasized the "larger picture" within which researchers should be viewed as a trusted entity within society. He emphasized the importance of the objective of science to contribute to the public good. Every encounter with a potential subject should move us further toward affirming the value of scientific research and building relationships with people. Individual rights and the collective good are both important to consider.

Dr. Lavery agreed with Dr. Resnik's point. He observed that we tend to assume that the determinates of trustworthiness are research outcomes, but in fact the experience of those affected, and the way that experience is communicated through their networks, are also critical. Despite this, we pay minimal attention to the participants' experience.

Session II: Do IRBs Have a Role in the Review of Third-Party Research Risks? If So, When?

Session II Overview and Introduction of Speakers

- *Moderator:* Leslie E. Wolf, J.D., MPH; Distinguished University Professor and Professor of Law, Georgia State University College of Law and School of Public Health

Prof. Wolf said the second session would focus on the role of the IRB, including boundaries, challenges, and opportunities in addressing third-party research risks. What can they do, and what can they not do, to address these risks?

Do Research Risks to Third Parties Require a Different Conceptual Approach?

- Jonathan Herington, Ph.D.; Assistant Professor of Philosophy, University of Rochester

Dr. Herington addressed the theoretical foundations for dealing with third-party risks, arguing that they should not only be addressed within the context of interpersonal ethics but also within the larger context of the principle of justice.

He noted that such risks are pervasive. There are third-party risks in studies with human subject participants, such as the HIV/AIDS or genomics studies mentioned early. Also, people's safety may be at risk in studies that do not have any identified human subjects, such as gene-driven field trials, gain of function studies, or geoengineering. Studies without identified participants may also cause harm by the misuse of their results (for example, by the way in which socially sensitive health disparities related to race and drug use are described). There are inductive risks stemming from trial size and p-value choice. Finally, third parties can be harmed by choices in how research funding is used (for example, research to find fossil fuels vs. research on renewable resources). Studies can be unsafe or their results can be misused. The way the study is designed can build in injustice before it starts.

A standard approach to human subjects research protection focuses on *individual* subjects, seeking a minimization of risks and maximization of benefits for each individual. Informed consent is sought from each individual participant. A favorable risk-benefit ratio is understood to require that risks be minimized, and benefits maximized, for individuals. This approach does not require consideration of the long-term social implications of research – in fact, this is explicitly discouraged by federal regulations. IRBs are asked not to consider how results might be misused. There is an implicit presumption in favor of the "social value" of research.

The speaker pointed out that risks to which subjects have consented can be displaced to other subjects when individuals withdraw from studies or when certain groups are excluded. For identifiable third parties, risks to them can be resolved by excluding the linked participant. However, this may displace the risks to other third parties. For instance, in a low-resource setting, excluding a child from a study may mean the loss of benefits for that child's family. For unidentifiable third parties, risks may be resolved only by cancelling the study altogether – but this, too, may simply displace risks. For example, if a human challenge study is cancelled because it poses too high a risk to possible subjects, losing that knowledge might increase risks for people living with the disease.

Dr. Herington held that justice cannot be achieved simply by extending human subjects protection to the community. It would be possible to seek a favorable risk-benefit ratio for the community as a whole and seek community consent through various means of consensual decision-making. However, there are problems with this approach. These include:

- Scientific disagreement about the scale of risks and benefits offered by the research.
- Community disagreement about the value of benefits and risks.
- Expert risk-benefit analysis fails to honor the autonomy of community members. Absent clear (political) authority, decisions on behalf of the community lack legitimacy.
- The difficulty of informing all affected parties.
- Disagreement about the risks among individuals.

Given these concerns, a procedure for adjudicating disagreement is essential. All preferences

cannot be satisfied, yet dissenting individuals cannot be excluded without stopping the study.

Justice as a lens. The speaker posited that the concept of justice could replace that of ethics as a "new theoretical lens." Ethical principles assume that affected persons are identifiable individuals, ignore population-level harms and benefits, and fail to consider the effect of other research studies. The principle of justice, on the other hand, assumes that all (or almost all) persons in society are affected by research, focuses on the distribution of harm and benefits within the population, and is sensitive to portfolios of research and collective actions. This approach would change the kinds of considerations taken into account as research is planned and the nature of the questions asked before proceeding. To determine whether something is just, we need to consider:

- What *kinds* of risks do individuals get to "veto"? Possible conclusions might be those that affect bodily autonomy, matters of personal conscience, and democratic equality (i.e., no research should proceed that undermines equal citizenship).

- What *level* of risk is reasonable? Should benefits outweigh risks for each individual, or in the aggregate? Should no one be any worse off, even if some are better off?

- What *distribution* of risk is appropriate? Often risks target those who are worse off, but benefits accrue to those who are well off. How can long-term wellbeing be maximized for the people as a whole? Should research that benefits those most in need be prioritized?

Decisions should be justified from the perspective of the justice lens.

Dr. Herington concluded his remarks by stressing that standard accounts of human subject protection have structural deficits when we apply them to third-party risks. Risks to third parties are a pervasive part of research, and the standard approach, with its emphasis on individuals, is not an appropriate way to deal with socially distributed risks. Instead, theories of *justice* may provide the best tools to navigate issues related to third-party risks.

What if All Ethical Implications of Research Could be Taken Seriously? Insights and Opportunities from Stakeholder Theory

- Jim Lavery, Ph.D.; Conrad N. Hilton Chair in Global Health Ethics; Professor, Hubert Department of Global Health, Rollins School of Public Health, Emory University

Dr. Lavery suggested considering third parties as stakeholders in research. He believes that the logic of stakeholder engagement may offer a novel way to understand and address the complex social, political, and economic issues related to third parties, with IRBs functioning as the drivers of organizational learning.

The speaker pointed out that many problems in research ethics are "wicked problems" (Rittel & Webber, 1973); they are similar to climate change in that they cannot be stated in a definitive way or reach a final solution. The standardized forms of reasoning with which we approach these problems is inadequate to their complexity.

Often, as in several cases of global health research cited by the speaker, it is impossible to make sense of the ethical obligations of funders, research institutions, implementation partners, and investigators by looking solely at what is required to protect individual research participants. In the cases presented, challenges were approached through the logic of stakeholder theory, which emphasizes that a stakeholder is an individual or organization who might be affected in a specific way by a given research project – i.e., who might have some interests at stake. The purpose of stakeholder engagement is to discover, through dialogue and deliberation, who is a stakeholder for a given research project.

It is often only through dialogue and deliberation that these interests become obvious and the nature of the researchers' and research institutions' obligations become clear. If a study runs the risk of setting back the interests of a third party (i.e., harming them), then that third party is a stakeholder, whether or not the current regulatory scheme views the issue in those terms. And there is, at least, a *prima facie* ethical obligation to avoid, or minimize that harm, regardless of how that individual or organization is categorized by the regulations.

Community engagement is fundamentally about engaging with the community of stakeholders, rather than with groups of people who simply share a common geography or some form of pre-existing association independent of the research. In effect, each study creates a new "community" of stakeholders, which has been characterized by King et al. as the "human infrastructure" of research (2014). Discerning who is a stakeholder and engaging with the community of stakeholders—including "third parties"—for a given study can help to fulfill three core ethical goals of stakeholder engagement:

1. *Identify and respond to non-obvious stakeholder interests and contextual factors.* This includes generating insights about what interests are at stake and the potential value for stakeholders resulting from proposed research.

2. *Extend respect beyond the individual.* Researchers can generate trustworthiness and fairness in both process and partnerships; design and adopt approaches that safeguard stakeholder interests; and respond to the community.

3. *Build legitimacy for the research project*. Researchers create opportunities for dialogue and deliberations with stakeholders, examine assumptions, and establish a "human infrastructure" based on relationships with stakeholders.

From the perspective of stakeholder theory, the social value of research is not just about the quality of the results or implications of the research. Rather, it is an aggregate measure of how well research creates value for all relevant stakeholders (for example, by protecting them from

harm or responding to their interests in a constructive way).

Third parties in research are those who have some interests at stake in the conduct and/or outcomes of the research or intervention. They may be harmed by the conduct and/or outcomes of research (either incidentally or wrongfully). The strength of researchers' ethical obligations to third parties is determined primarily by the nature of the interests at stake and how they are likely to be affected by the conduct or outcomes of the research. Dr. Lavery cited Anna Durbin, a Principal Investigator at the Johns Hopkins Center for Immunization Research, on her approach to boosting diversity in COVID-19 clinical trials: "We make a point to say that we aren't just coming in to do a trial and then leaving, so we ask, 'What can we bring to the community besides these trials that is going to last? How can we help with getting people engaged in health care?'"

Third parties can provide critical insights about how research programs might increase their value for communities or society by illuminating specific opportunities to create value. Dr. Lavery cautioned that adopting too narrow a concept of who should be considered a third party (or a stakeholder) can impoverish the opportunities for learning that make research relevant, responsive, and valuable. IRBs can drive learning by encouraging their institutions and their investigators to view third-party issues as opportunities for organizational learning and collaborative problem-solving with stakeholders. This will improve the value of the research that is conducted under the auspices of their institutions.

Why (and How) Bystander Protections Make for Good Ethics and Policy

- Jonathan Kimmelman, Ph.D.; James McGill Professor of Medical Ethics, McGill University

Dr. Kimmelman first started thinking about third-party risk (bystander risk) as a side project related to his work on the ethics of gene transfer (gene therapy). Gene therapy often uses recombinant viral vectors that can shed in a person's excretions and present risk to third parties – a problem he initially thought of as small and manageable. He wondered whether human protections policies had anything to say about evaluating risk and benefit for bystanders and published two articles on the subject (Kimmelman, 2005; Kimmelman, 2007). He identified numerous arenas in which research presents third-party risks. He defined bystander risk as "the prospect of harm to identifiable individuals or groups of individuals, other than research subjects themselves, that is a direct consequence of the research activities (as opposed to the knowledge such research activities generate and their application)."

At the time, literature focusing on this topic was lacking. However, an increasing number of research types are now identified as presenting some form of risk to third parties. Despite this reality, related issues are seldom on the radar of researchers, IRBs, and others, and there is little guidance on policymaking to address these risks.

The speaker gave several examples in which third parties are affected by research design. Donor intervention studies might require cooling an organ to enhance its viability, which may

affect organs transferred to non-subjects. Such research might also affect the order in which people waiting for organs become eligible to receive them. Any trial conducted in a low-income setting could conceivably marshal equipment for study purposes that then becomes inaccessible to others. HIV cure studies, which have already been discussed, provide another example. At some level, he argued, it is possible that almost all research involves at least a bit of risk to third parties. In the examples just cited, however, individuals and communities affected are identifiable, the risks are potentially large, and it is difficult to come up with good reasons not to confer some level of protection on third parties.

Many research ethics policy statements address third-party risks, but in a piecemeal fashion (e.g., the Common Rule; CIOMS, 2016; National Commission, 1978; National Research Council, 2003; Canadian Institutes of Health Research, 2018). Common protections in trials of various types include the exclusion of lactating mothers, use of barrier contraception, quarantine, and the recruitment of incipient volunteers. In general, however, Dr. Kimmelman held that common protections for third parties in trials represent "inchoate" notions of what care for them might mean.

Principles and approaches. In principle, Dr. Kimmelman held, it is difficult to see how the three principles established in the Belmont Report (National Commission, 1978) would *not* extent to bystanders. *Respect for persons* requires consideration of involuntary exposures. *Beneficence* might be increased by third-party oversight of risks and benefits. *Justice* demands that burdens should not fall disproportionately on disadvantaged populations and that communities targeted for research are selected fairly.

Dr. Kimmelman argued that the integrity of the research enterprise requires analysis of possible harms to third parties. Triggers for third-party concerns are not all based on the magnitude of risk as perceived by researchers; some harms are of particular concern to the public (for example, harms to populations with cultural significance or to children).

What we really care about when we do medical research is healthcare and what we care about with healthcare is enabling equitable and efficient delivery of healthcare. This goal cannot be achieved without a steady flow of evidence into the healthcare system. Generation of such evidence is not merely about physicians interacting with patients but also about patients interacting with various other actors in this enterprise and placing credence in research findings. One, therefore, wants to configure all aspects of research in a manner that inspires a high level of confidence among patients that researchers, their institutions, and relevant federal agencies will protect their welfare and interests and are responsive to their needs. Addressing bystander risk is part of this process. Research ethics should be especially vigilant in addressing risks and inequities that would harm this confidence.

IRBs can play a crucial role by signaling to researchers that they need to pay attention to risks to third parties. The IRB is the only institutionalized mechanism for overseeing research that seems capable of playing this role. In response, researchers should incorporate provisions in protocols to address third-party risks, including strategies for exploring and disclosing such risks. For reasons of administrative efficiency, however, the IRB mandate on third-party protections should be narrowly bounded. Three questions are germane:

- Is there bystander risk?
- Are there legitimate and effective mechanisms in place to address and manage that risk?
- If not, assess the management plan and ensure it is revised to take this risk into account.

Where necessary, research might be prohibited, or protocols might be modified to better take implications for third parties into account. Community disclosure could be required. Third parties might be reclassified as subjects and asked to give consent for the research. Finally, harms to third parties should be tracked and reported.

Reviewing Third-Party Risks: A Proposed Framework for IRBs (and Researchers)

- David B. Resnik, J.D., Ph.D.; Bioethicist and Senior Ethics Specialist, Adjunct Professor of Philosophy and Religion, North Carolina State University; National Institute of Environmental Health Sciences, National Institutes of Health

Dr. Resnik noted that the ethical basis for addressing risks to third parties stems from the key principles articulated in the *Belmont Report* – respect for persons, beneficence, and justice. From a legal perspective, tort liability for negligence provides a framework that asks, in reference to standard of care, what a reasonable person would do and whether risks to others are reasonable.

Dr. Resnik defined a third party as an identifiable person, group of people, or organization who is not a research subject or investigator but may be directly impacted by the research, such as:

- A fetus or breastfeeding child for a woman in a clinical trial,
- Family/household members of a participant who receives a vaccination that can be spread to others,
- Family/household members of a participant who receives radioactive iodine therapy,
- Children who might get access to medication sent home with the patient/participant,
- Children who might be impacted by pesticide spraying in the home for an asthma study,
- A community participating in a community-based research project, or
- An employer who gives permission for researchers to study workers' health.

Examples of such risks include any of the following:

- Physical, chemical, or biological risks, such as exposure to chemicals, drugs, radiation, infectious agents;
- Psychosocial risks, such as stress, loss of privacy or confidentiality, discrimination or bias; or
- Legal or financial risks, such as an occupational health study that could result in

business losses.

What steps can be reasonably taken to minimize third-party risks? The speaker gave several examples, but noted that solutions sometimes raise ethical questions themselves:

- *Including provisions in the protocol or study procedures to minimize risks to others,* such as instructing participants who receive radioactive iodine on how to eliminate it from their body quickly, clean it up, and ensure that they have a form of non-public transportation home. Another example is the need for precautions to keep children from getting access to medications taken home.

- *Informing the participant about risks to third parties and asking the participant to take appropriate steps to reduce these risks.* An example is cautioning participants receiving iodine therapy about not exposing others (though the speaker wondered whether it is really appropriate to put such responsibilities on participants).

- *Excluding people from a study to protect third parties*. Pregnant women may be excluded from a clinical trial to protect the fetus, for example, though doing so raises issues of justice and access to research opportunities.

- *Obtaining consent from third parties*. Researchers can seek permission from a community to do community-based research or from a business to do research on the health of its employees (but what if they say no?).

Reasonableness of risks. Reasonableness, Dr. Resnik said, is an "all-things-considered, normative, moral judgment": Is this proposed approach ethical or moral, all things considered? It is not the same as an instrumental approach that asks whether the means justifies the end. The perspective changes as you consider the risks you might be willing to take for yourself as opposed to those you might impose on others.

Three key questions arise in determining whether or not risks to third parties are reasonable:

- Are risks to third parties reasonable in relation to the value of the research?
- Are the risks to third parties more than minimal, i.e., more than the risks of daily life?
- Is the research too risky?

Dr. Resnik cited several considerations in making this determination:

- The social benefit of the activity, e.g., automobile driving;
- The value of human freedom to engage in the activity, e.g., producing videos, films, books, etc. with violent or disturbing content vs. freedom of expression;
- The fairness and justice of distribution of risks, for example, indigenous population or farmworkers bearing a disproportionate burden of risks;
- The fairness of the processes or procedures used to impose risks, such as community engagement;
- Epistemic responsibility, that is, basing risk assessment on the best available evidence

rather than gut feelings; and
- Consistency in decision-making and policy.

Are IRBs the Right Oversight Bodies for Protecting Third Parties?

- Daniel M. Hausman, Ph.D.; Research Professor, Center for Population-Level Bioethics, Rutgers University

Dr. Hausman began by defining third-party risk, slightly adapting Dr. Kimmelman's definition: "The risk of harm to identifiable individuals or groups of individuals, other than research subjects themselves, that is a direct consequence of the research activities" (adapted from Kimmelman, 2020). He stated that:

- Bystanders should be protected from significant risks and losses caused by the conduct of scientific research.
- The principles of respect for persons, beneficence, and justice all justify protecting bystanders.
- Without information or consent, bystanders arguably have at least as strong a claim to protection as do research subjects.
- Protection of bystanders is a concern of research ethics.
- Harms to bystanders can undermine confidence in research.

The speaker noted that when the framework shifts from the consideration of risk to the possibility of serious harm, the determination becomes much more difficult.

The speaker saw several considerations in favor of the use of the IRB as the oversight body responsible for protecting third parties in research. The approach makes use of an existing institution and economizes on effort. Also, there is no obvious alternative.

However, there are also good reasons *not* to place IRBs in this role:

- Third-party risks do not arise only in research, let alone research on human subjects.

- Such risks raise general questions in political philosophy concerning the distribution of risks and benefits of scientific research. Even if you engage in processes for community consultation, an individual's viewpoint may not be represented.

- Different principles apply to experimental subjects and third parties. IRB members may not distinguish them.

- IRBs are already heavily burdened; additional tasks may interfere with the conduct of research.

- Assigning this function to IRBs ensures variation in how it is handled.

Dr. Hausman said these were "powerful considerations," and if third-party protection were to be added to IRBs' responsibilities, he suspected they would not address these issues well. However, he asked again: What other institution can do the job?

Session II Panel Discussion

Who should protect third parties? Prof. Wolf asked panelists to consider in more depth whether IRBs are the right body to address third-party risks. Is there another body that can step in? Does the IRB have the authority to address these risks? She highlighted the possibility of "mission creep," as well as the possibility that researchers and community members will be angry that research they care about is *not* approved (Tuskegee in reverse!) (Malone, Yerger, McGruder, & Froelicher, 2006; Wolf, 2010).

Dr. Lounsbury said that some institutions are already finding ways to protect at least some second and third parties. Biosafety committees protect many people. Occupational health and safety committees protect lab workers. Some categories of risk are addressed in the context of clinical care. We need to focus on the categories of risk that are not addressed through existing mechanisms.

Dr. Resnik also expressed concern lest the task of ensuring that third-party issues are addressed fall to legal counsel and risk managers, who are prone to making very conservative decisions that could impede research. If IRBs don't take this on, the legal risk management people will undertake to protect the institution at all costs, including the cost of not doing important research.

Prof. Nelson agreed with the pros and cons that Dr. Hausman expressed in regard to IRBs addressing the problem of third parties. He noted that the authority of the IRB stems from the applicability of federal regulations. Over half of the examples he presented earlier would be categorized as not being human subjects research and therefore not subject to the regulations at all, while perhaps a majority of the rest would qualify for exemptions, particularly with the expanded exemption categories in the revised Common Rule. In short, many studies that pose risks to third parties would not come under the purview of IRBs without further revisions to the Common Rule. Further, he noted that IRBs function well when they have a clear process to follow, and the lack of clear guidance in the cases discussed suggests that they are unlikely to address these issues very well.

Prof. Fernandez Lynch observed that IRBs are not able to address the complexity of third-party issues in part because they are facing so many challenges already. This issue may present an opportunity to re-envision the role and responsibilities of the IRB. Dr. Eyal suggested that focused training and guidance might help IRBs better handle more challenging cases. There are many possible ways to assist them short of revising the regulations.

Prof. Shah wondered whether Dr. Lavery's remarks pointed to the need to broaden our concept

of third-party risks.

Dr. Herington suggested that a typology of third-party risks would be helpful and that the IRB's role in adjudicating these risks would depend on the structure of the risks presented in specific studies. Are there direct participants? Are bystander risks linked to human participants in the study? Are third parties identifiable or not? The IRB can and should be involved in addressing risks that are linked to participants and identifiable third parties. It is less clear that they should be involved in studies that do not have direct participants. A clear typology can help IRBs make good decisions about whose job it is to address possible risks.

Coordinating with partners. Dr. Kimmelman suggested that IRBs should delegate as much of the responsibility to deal with this issue to other groups as possible. He noted that third-party risks are a broader sphere than the narrower range of ethical concerns IRBs are used to dealing with. For example, healthcare institutions may have responsibilities that supersede the roles of individual researchers.

Prof. Wolf observed that IRBs do have partners with specific responsibilities. How do they negotiate roles with these partners? How does coordination work? Dr. Kimmelman responded that there is no simple answer to the problem of the division of labor. It falls to the IRB to make an initial assessment about the competency, legitimacy, and functionality required to address the risks posed in a particular study.

The role of community. Prof. Wolf noted that, as a country, we have spent the last 18 months looking at issues of justice. Does concern for justice require a new framework?

Dr. Lounsbury said community consent is crucial in achieving justice. We need greater awareness of risks and benefits as seen from the community perspective. He stressed the importance of inviting the community in and working with them in a collaborative way. However, we need to be clear about why we are doing so. Is our concern epistemological? Are there ethical values or ideologies in play? Are we trying to share policy differently and empower marginalized voices? (See Trickett & Ryerson Espino, 2004).

Dr. Lavery agreed, noting that we tend to look at community in ways that are overly strict and limited. Research creates communities beyond the existing one – a community of interests that stems from the research itself.

Dr. Hausman was more skeptical about the extent to which collaborating with communities can help researchers address third-party risks. There are many kinds of community; some have an authority structure, clear interests in the research, and people to negotiate with; others will have nothing like that to offer and there might be no real community interest in the research. He suggested that researchers should be skeptical about offering power to the community and think carefully about how interactions with them can be valuable. Dr. Resnik also expressed concern about putting effort into consulting with the community when it is unnecessary. In some cases, in this era in which there is a strong anti-science movement, "it can just lead to trouble."

Dr. Krishnamurti observed that some funding agencies require community engagement and

dissemination of information to community members. She felt that more problems were likely to be avoided than created by dealing with community members in transparent and accountable ways.

Education and communication. Prof. Wolf invited the panel members to consider how education and communication might help address third-party risks.

Dr. Lavery stressed the role of funders in making community consultation more meaningful. Too often, stakeholders are consulted only after protocols and budgets are finalized, so there are no concrete ways to actually respond to stakeholder interests once they have been identified. This can result in stakeholders' perception that engagement or consultation is just an empty exercise that is not truly responsive to their interests.

"Community consultation can be messy," Dr. Resnik observed. It has worked well in hearing indigenous populations on issues related to their exposure to arsenic in groundwater. Other issues are more controversial, such as field trials of transgenic mosquitos driven by environmental groups outside the community. Communication is critical.

Dr. Colby commented that Community Advisory Boards for people living with HIV/AIDS are often engaged, knowledgeable groups. He has observed that people living with a disease often have a higher tolerance for risk than IRBs. People at risk of contracting the disease often have a very good idea of what their risk is as a result of good public communication.

Prof. Wolf noted that there are many other ways to involve communities. She has been impressed by strategies used by the Department of Defense to involve stakeholders, especially in peer review. A panel member observed that Naomi Scheinerman offers useful insights on deliberative democracy and ways to encourage the expression of multiple voices (e.g., Scheinerman, 2021).

Another panelist commented that the Tarasoff case, which resulted in clarifying the duty to warn on the part of people whose professions may make them aware of threats to third parties, emphasized the need to protect vulnerable individuals or groups that could not otherwise protect themselves. Is this a helpful framework to expand our understanding of people outside the bounds of the kinds of risk we usually consider?

Dr. Herington said the "reasonableness" standard was helpful. When persons who may be harmed are identifiable, there are specific tools we can use to consider risks and establish thresholds. This is different from the challenge of anticipating risks to people who cannot be identified in advance, such as all possible sexual partners for people enrolled in an HIV/AIDS cure study.

Group harms. Prof. Wolf asked the panelists to consider aspects of the typology that is needed. What about long-term impacts and harms to groups? Do these not fit in the models we have been discussing?

Dr. Resnik said some groups can be clearly identified. These include cohesive populations

located in specific areas with well-defined constituencies. Another panel member observed that working with Community Advisory Boards can help identify risks that would otherwise be unknown. One example is the multiple risks faced by investigators entering homes after Hurricane Katrina. Community consultations identified many of these risks (for example, dangerous living conditions and bomb threats) so that investigators could prepare for them.

Dr. Herington stressed the importance of considering how research findings might stigmatize a vulnerable group. Even if IRBs are not the right review mechanism, researchers should consider such harms as part of study design. Prof. Nelson noted that the Havasupai case is a classic example of group harm. Prof. Shah said IRBs can identify problems like this even if they can't solve them; sometimes they can refer them to others to address. Prof. Wolf agreed that it was often helpful to flag such issues even if the IRB cannot resolve them.

Dr. Lavery said that concepts of harm and risk should be distinguished. It is important not to assume the research team can identify such harms on its own. When a restaurant is being inspected as part of a study, the restaurant as a corporate entity might have an interest in how this is done. Dr. Hausman observed, however, that it is not always a bad thing to harm a group. In some cases, driving a restaurant out of business might be a good thing.

Research on third-party issues. Prof. Wolf asked what research is needed to move the field forward to better address issues related to third-party protections. She heard the need for a typology of risks, tools for IRBs, and training for IRBs. What do we not know? What would be helpful?

Dr. Eyal stressed the importance of not trying to "jump in and create a whole draconic system" before there is enough clear evidence to determine what is needed.

Prof. Fernandez Lynch suggested encouraging researchers to include in their submissions to the IRB the answers to key questions: Are there relevant third parties? How do you think about them? What is your plan to protect them from research risks?

Dr. Kimmelman suggested that while we tend to be preoccupied with the period in which the protocol is being written, there may be issues that arise in the course of the study. Safety reporting may be insufficient. Unless you are looking for specific issues, you may not see them to report them. A greater emphasis on collecting information on third-party risks and harms is needed so that we know what is actually happening.

Dr. Lavery pointed to the tendency to forget that the Common Rule is designed to hold institutions responsible for research conducted under their auspices. Institutions need to support IRBs in ensuring third-party issues are addressed.

Dr. Herington saw the need for a "whole separate conversation to be had about what kinds of science we should be doing and not doing." He opined that there are probably ways that discussion intersects with this one.

Prof. Shah said that terminology issues should be addressed so that it is clear everyone is

talking about the same set of issues (most obviously, bystanders vs. third parties). This might help move the body of research forward more productively. Dr. Lavery cautioned, however, that clarifying terminology should note be done in a way that encourages people to ignore those who don't "fit into the box," which is effectively what the "third-party" language currently does.

Closing

Dr. Lau thanked all the speakers for exceeding the expectations of OHRP staff and the audience. A report summarizing the presentations and discussion will be available shortly at the OHRP website. Finally, she encouraged people to visit the website for OHRP's Division of Education and Development, which offers numerous free resources.

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SPEAKER BIOGRAPHIES

Session I

Nir Eyal, *PhD (Moderator)*
Henry Rutgers Professor of Bioethics, Director of the Center for Population-Level Bioethics (CPLB), Department of Health Behavior, Society and Policy, Rutgers University

Nir Eyal is the inaugural Henry Rutgers Professor of Bioethics at Rutgers University. He founded and directs Rutgers's Center for Population-Level Bioethics, with appointments at the School of Public Health and the Department of Philosophy. Dr. Eyal's work covers many areas of research ethics and population-level bioethics, including ethics in emerging infection trial vaccine trials, ethics of high-risk trials, and the ethics of disaster response. Eyal's work appeared in Science, PNAS, NEJM, Lancet, BMJ, and the leading bioethics venues. He is a coauthor of a WHO report, and has co-edited many volumes and journal symposia, as well as the Oxford University Press series Population Level Bioethics. Eyal is the recipient of multiple awards from NIH, Wellcome, NSF, and other sources. He edited three journal symposia and wrote multiple articles on the problem of protecting "third parties" or "bystanders" in medical and scientific research.

Daniel Nelson
Emeritus Director, Human Research Protocol Office, U.S. Environmental Protection Agency, Emeritus Professor of Social Medicine and Pediatrics, University of North Carolina at Chapel Hill

Recently retired, Daniel Nelson is Emeritus Director of the Human Research Protocol Office for the U.S. Environmental Protection Agency, and Emeritus Professor of Social Medicine and Pediatrics at the University of North Carolina-Chapel Hill. Over the course of his career, Nelson played a leading role in national initiatives that shaped the field of human research protections, serving as president of the Applied Research Ethics National Association; charter member of the Council for Accreditation and site visitor for AAHRPP; charter member of the Council for Certification of IRB Professionals; and consultant to the federal OHRP. For ten years he chaired a subcommittee of the Secretary's Advisory Committee on Human Research Protections (SACHRP), advising DHHS on the regulations that govern this area. In 2013 Nelson was honored by Public Responsibility in Medicine and Research (PRIMR) with the ARENA Legacy Award, for leadership and contributions to the field of research ethics.

Donn Colby, *MD, MPH*
Research Physician, US Military HIV Research Program (MHRP)

Dr. Donn Colby is a Research Physician at the U.S. Military HIV Research Program (MHRP). Based in Seattle, WA, he supervises collaborative studies with Joint Base Lewis-McChord (JBLM) in Washington State and contributes to clinical protocols implemented in Asia. Prior to joining MHRP in 2019, he was co-investigator on the RV254 trial of acute HIV infection at the Thai Red Cross AIDS Research Centre in Bangkok, Thailand. Dr. Colby received his B.A. in Biology at Johns Hopkins University and his M.D. at the State University of New York at Stony Brook. He did his internal medicine residency training and Masters in Public Health at the University of Washington in Seattle. Dr. Colby's has published extensively on the epidemiology of HIV in Southeast Asia, clinical outcomes among people living with HIV, the implementation of preexposure prophylaxis (PrEP), and clinical trials aiming to cure HIV infection.

David W. Lounsbury, *PhD*

Associate Professor, Epidemiology & Population Health, Division of Health Behavior Research and Implementation Science, Albert Einstein College of Medicine, Bronx, NY USA

A community psychologist and psycho-oncologist, Dr. Lounsbury's domestic and international research is directed towards implementation of health services interventions and community-based interventions in prevention and control of chronic health illnesses, including cancer, diabetes/ obesity, and HIV/AIDS, with a focus on the needs of medically underserved populations. He applies ecologically-grounded social science methodologies, such as participatory action research and system dynamics modeling, as a means to explore and assess complex, multi-level, problems in health care delivery.

Seema K. Shah, JD

Founder's Board Professor of Medical Ethics, Associate Professor of Pediatrics, Lurie Children's Hospital & Northwestern University

Seema K. Shah, JD is the Founder's Board Professor of Medical Ethics and the Director of Research Ethics at Lurie Children's Hospital. She is an Associate Professor of Pediatrics at Northwestern University Feinberg School of Medicine, with a courtesy appointment at Northwestern's Pritzker School of Law. Professor Shah is an international expert in the fields of pediatrics and global health research ethics, as well as on legal and ethical issues in the determination of death. She has published more than 70 articles in the medical, bioethics, and legal literatures and is the co-author of a book on Research Ethics Consultation. She has lectured on these topics around the world and had numerous media mentions and appearances, including in the Wall Street Journal, the New York Times, and PBS NewsHour.Professor Shah attended Stanford University for her undergraduate and law degrees and completed a fellowship in bioethics at the National Institutes of Health (NIH) Clinical Center. She clerked in federal district court in Sacramento, California. Shah was previously on faculty at the University of Washington/Seattle Children's Hospital and at the NIH Clinical Center Department of Bioethics. Finally, Professor Shah has a distinguished record of service, including chairing an NIH committee on ethical considerations in conducting Zika virus human challenge trials and serving as an expert member of a World Health Organization working group to develop key criteria for human challenge trials to address COVID-19 and beyond.

Holly Fernandez Lynch, *JD, MBe*

John Russel Dickson, MO Presidential Assistant Professor of Medical Ethics, Department of Medical Ethics and Health Policy, Perelman School of Medicine (PSOM), University of Pennsylvania, Founder and Chair, The Consortium to Advance Effective Research Ethics Oversight (www.AEREO.org)

Holly Fernandez Lynch, JD, MBE, is the John Russell Dickson, MD Presidential Assistant Professor of Medical Ethics in the Department of Medical Ethics and Health Policy at the Perelman School of Medicine, University of Pennsylvania. Her scholarship focuses on clinical research ethics, access to investigational medicines, Food and Drug Administration policy, and the ethics of gatekeeping in health care. She is founder and co-chair of the Consortium to Advance Effective Research Ethics Oversight (AEREO), which aims to understand, evaluate, and improve IRB quality and effectiveness through empirical research. Prior to joining Penn, Professor Fernandez Lynch was Executive Director of the Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics at Harvard Law School. She previously worked as an attorney in private practice focused on pharmaceuticals regulation at Hogan & Hartson, as a bioethicist at the NIH's Division of AIDS, and as a senior policy and research analyst with President Obama's Commission for the Study of Bioethical Issues.

Tamar Krishnamurti, *PhD*

Assistant Professor of Medicine and Clinical & Translational Science,
Division of General Internal Medicine, University of Pittsburgh

Tamar Krishnamurti, PhD is an Assistant Professor of Medicine and Clinical and Translational Science at the University of Pittsburgh. Dr. Krishnamurti draws on (and develops) methods in the social and decision sciences, working with cross-disciplinary experts and community members, to examine problems at the intersection of health, risk, technology, and the environment. Her most recent research focus has been on risk identification, communication, and intervention for maternal health using mobile technologies. At the University of Pittsburgh, Dr. Krishnamurti leads the Behavioral Health arm of the Center for Research on Behavioral Health, Media, & Technology and is a co-founder of the FemTech Collaborative, housed within the Center for Women's Health Research and Innovation.

Session II

Leslie E. Wolf, *JD, MPH (Moderator)*

Distinguished University Professor and Professor of Law,
Georgia State University College of Law and School of Public Health

Leslie Wolf is Distinguished University Professor and Professor of Law at Georgia State University College of Law and the School of Public Health. She served as interim dean of the College (2019-2021) and as director of the Center for Law, Health & Society (2014-2019). Professor Wolf is a leading national scholar in health law, public health and ethics, with a focus on research ethics. She has conducted research on confidentiality risks and protections with a particular focus on Certificates of Confidentiality, research involving biospecimens, conflicts of interest, and IRB guidance, which has been funded by the National Institutes of Health and the Greenwall Foundation. From 2016-2021, Professor Wolf was a member of the Secretary's Advisory Committee on Human Research Protections (SACHRP). She continues to serve on SACHRP's Subcommittee on Harmonization. She previously served on the Centers for Disease Control and Prevention's Ethics Subcommittee to the Advisory Committee to the Director.

Jonathan Herington, *PhD*

Assistant Professor of Philosophy, University of Rochester

Jonathan Herington is an Assistant Professor of Philosophy at the University of Rochester. His research focuses on the political philosophy of science, health and technology. He applies the tools of political philosophy to issues arising in research ethics, the ethics of machine-learning algorithms, public health ethics, and environmental governance. Previously he was an Assistant Professor in the Department of Philosophy at Kansas State University and a Research Fellow in the Medicine, Ethics, Society and History unit of the University of Birmingham. He completed his PhD in the School of Philosophy, at the Australian National University.

James Lavery, *PhD*

Conrad N. Hilton Chair in Global Health Ethics, Professor, Hubert Department of Global Health, Rollins School of Public Health, Faculty of the Center for Ethics, Emory University

Jim Lavery is the inaugural Conrad N. Hilton Chair in Global Health Ethics, Professor in the Hubert Department of Global Health in the Rollins School of Public Health, and Faculty of the Center for Ethics, Emory University, Atlanta, Georgia. Prior to Emory he held positions at the National Institutes of Health, and at St. Michael's Hospital and the University of Toronto. He is a Fellow of the Hastings Center and the 2017 recipient of the Global Forum for Bioethics in Research Award for Contributions to Progress in International Research. He is a member of the Board of Directors of the Council for Health Research for Development (COHRED) USA, Chair of the Scientific and Technical Advisory Committee of the Health Campaign Effectiveness Coalition at the Task Force for Global Health in Atlanta, and a member of the Bioethics Advisory Panel of Pfizer, Inc.

Jonathan Kimmelman, *PhD*

James McGill Professor of Medical Ethics, McGill University

Jonathan Kimmelman, PhD, is James McGill Professor of Biomedical Ethics at McGill University, and directs the Biomedical Ethics Unit as well as his own research group, STREAM (Studies in Translation, Ethics and Medicine). Kimmelman's research centers on ethical policy and scientific dimensions of clinical development. Kimmelman received the Maud Menten New Investigator Prize (2006), a CIHR New Investigator Award (2008), a Humboldt Bessel Award (2014), and was elected a Hastings Center Fellow (2018). He has sat on various advisory bodies within the U.S. NHLBI and NIAID, served for four tours of duty on U.S. National Academies of Medicine committees, and chaired the International Society of Stem Cell Research Guidelines for Stem Cell Research and Clinical Translation revision task force 2015-16. His research has been covered in major media outlets, including NPR's All Things Considered, STATNews, and Nature. Kimmelman is deputy editor at Clinical Trials, and associate editor at Cell Med.

David B. Resnik, *JD, PhD*

Bioethicist and Senior Ethics Specialist, Adjunct Professor of Philosophy and Religion, North Carolina State University, National Institute of Environmental Health Sciences, National Institutes of Health

David B. Resnik is a Bioethicist at the National Institute of Environmental Health Sciences, National Institutes of Health. Dr. Resnik has an M.A. and Ph.D. in philosophy from the University of North Carolina at Chapel Hill, a J.D. from Concord University School of Law, and a B.A. in philosophy from Davidson College. Dr. Resnik was an Associate and Full Professor of Medical Humanities at the Brody School of Medicine at East Carolina University (ECU) from 1998 to 2004, and an Associate Director of the Bioethics Center at ECU and University Health Systems from 1998 to 2004. Dr. Resnik was Assistant and Associate Professor of Philosophy at the University of Wyoming (UW) from 1990 to 1998, and Director of the Center for the Advancement of Ethics at UW from 1995 to 1998. Dr. Resnik has published over 300 articles and 10 books on various topics in philosophy and bioethics and is a Fellow of the American Association for the Advancement of Science. He serves on several editorial boards and is an Associate Editor of the journal Accountability in Research.

Daniel M. Hausman, *PhD*

Research Professor, Center for Population-Level Bioethics, Rutgers University

Educated at Harvard, Cambridge, and Columbia Universities, Daniel Hausman taught at the University of Maryland, Carnegie Mellon, and for 32 years at the University of Wisconsin-Madison before accepting his current position at the Center for Population-Level Bioethics at Rutgers University. His research addresses methodological, metaphysical, and ethical issues at the boundaries between economics and philosophy, and is currently focused on the ethical appraisal of the use of cost-effectiveness information to allocate health care. The author of nearly 200 books and articles, Hausman also co-founded the journal, Economics and Philosophy with Michael McPherson. His most important books are The Inexact and Separate Science of Economics (1992), Causal Asymmetries (1998), Preference, Value, Choice, and Welfare (2012), Valuing Health: Well-being, Freedom, and Suffering (2015), and, with Michael McPherson and Debra Satz, Economic Analysis, Moral Philosophy and Public Policy. In 2009 Hausman was elected to the American Academy of Arts and Sciences.


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