AGENDA

Background: Common clinical practices might lack a robust evidence base if there have not been empirical interventional research studies to compare an array of available routine or standard treatment options. Clinical trials that study these “standard of care” interventions examine and compare treatments that fall within the range of what is considered usual clinical practice. The goal is to gather evidence that can be used when selecting a particular intervention. The Federal Policy for the Protection of Human Research Subjects, known as the “Common Rule,” governs the ethical oversight of human participation in research, including requirements for informed consent and procedures for research ethics review bodies, i.e., Institutional Review Boards (IRBs). Under the Common Rule, IRBs are responsible for overseeing clinical trials to ensure that the safety, well-being and rights of trial participants are protected. In addition, the IRB also oversees the process of obtaining informed consent, so that participants understand the risks and potential benefits of the trial before deciding whether to enroll. Recently, questions have arisen about the key aspects of standard of care trials, including how to define reasonably foreseeable risks, and how to include in the consent process enough information about the risks and benefits of being in a trial of standard interventions. The purpose of this workshop is to bring together key stakeholders to examine the ethical issues surrounding study design and informed consent for regulated research studies involving standard of care interventions.

Meeting objectives:

• Consider how risks associated with receiving standard of care interventions from a health care provider might or might not be distinguished from risks associated with participating in research that compares two standard of care interventions for a condition.
• Discuss criteria for identification of reasonably foreseeable risks associated with research studying standard of care interventions.
  o Highlight approaches for (a) identifying what constitutes evidence and (b) ascertaining whether the degree or extent of identified evidence informs the determination of reasonably foreseeable risk.
• Discuss issues pertaining to randomization of participants in research studying standard of care interventions, including whether and under what circumstances the act of randomization could be considered a risk to research participants.
• Explore the above outlined issues, and gaps and areas of uncertainty in the guidance available to the research community, with specific attention to the following:
o How researchers evaluate and characterize the above issues in designing research protocols comparing standard of care interventions.
o How Institutional Review Boards (IRBs) assess and exercise oversight of research studying standard of care interventions.
o How concepts relating to participation in studies involving standard of care interventions, including potential risks associated with receiving standard of care interventions and with research participation itself, are communicated with research participants.

DAY ONE: December 2, 2014

8:30 a.m. Opening Remarks

Workshop Chair: R. Alta Charo, University of Wisconsin

8:35 a.m. HHS Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care (Pre-recorded from October 2014 Secretary's Advisory Committee on Human Research Protections Meeting)

JERRY MENIKOFF
Office for Human Research Protections

9:15 a.m. Overview of Workshop Objectives

Workshop Chair: R. Alta Charo, University of Wisconsin

SESSION I: RANDOMIZATION OF PARTICIPANTS – DETERMINING AND COMMUNICATING RISKS

Session Objectives:
- Explore whether and under what circumstances the act of randomization could be considered a risk to research participants.
  - Discuss aspects of randomness in clinical practice outside a research trial.
- Consider how concepts relating to randomization might be communicated to study participants and how this might affect the informed consent process.
- Discuss implications for the review, conduct, and oversight of randomization in research studying standard of care interventions.

9:20 a.m. Overview of Session Objectives (5 min)

Session Chairs: Steven Hyman and Gregory Simon

9:25 a.m. Session Presentations
Cryptic Randomness within the Standard of Care

HAROLD SOX
Patient-Centered Outcomes Research Institute
Geisel School of Medicine at Dartmouth

Theory and Goals of Randomization in Standard of Care Interventions

SUSAN ELLENBERG
University of Pennsylvania

Randomization Alters Risks to Research Participants

NANCY KING
Wake Forest School of Medicine

Communicating about Randomization with Research Participants

MIRIAM KUPPERMANN
University of California, San Francisco

10:25 a.m.  BREAK (15 min)
10:40 a.m.  COMBINED PANEL

Panelists:
- Harold Sox, PCORI and Dartmouth Geisel School of Medicine
- Susan Ellenberg, University of Pennsylvania
- Nancy King, Wake Forest School of Medicine
- Miriam Kuppermann, University of California, San Francisco
- Vanessa Northington Gamble, George Washington University
- Bray Patrick-Lake, Duke Translational Medicine Institute
- Benjamin Wilfond, University of Washington
Panel Objectives:

- Address the following discussion questions *(45 min)*
  - How much randomness is present in the purely therapeutic context when providers choose among standard of care options?
  - How does this compare to the formal randomization of a prospective, randomized clinical trial? How is randomization implemented in standard of care research?
  - What difference (if any) does this make in the risks and potential benefits to the patient or study participant? Does randomization itself constitute a risk of research? If this depends on the specifics of the intervention or type of patient, please elaborate.
  - How do we ensure randomization procedures are effectively communicated to patients? If this depends on the specifics of the intervention or type of patient, please elaborate.
  - How can randomization in other domains (e.g., criminal justice domain) better inform us about implementing randomization in standard of care research?
- Discuss relevant areas of the guidance *(45 min)*

12:10 a.m.   **PUBLIC COMMENT** *(20 min)*
- Members of the public are invited to sign up to provide comments geared toward the session topic.

12:30 p.m.   **LUNCH** *(30 min)*

**SESSION II: METHODOLOGY FOR EVALUATING THE DEGREE OF RISK & DETERMINING RISKS THAT ARE REASONABLY FORESEEABLE**

Session Objectives:

- Highlight approaches and criteria for evaluating whether a risk is reasonably foreseeable.
- Consider how reasonably foreseeable risk is communicated and perceived by research participants and how this might affect the informed consent process.
- Discuss implications for the review, conduct, and oversight of research studying standard of care interventions.

1:00 p.m.   **Overview of Session Objectives** *(5 min)*

*Session Chairs:* R. Alta Charo and Clay Johnston
Session Presentations

Component Analysis Approach to Evaluating Risk

CHARLES WEIJER
University of Western Ontario

Ethical Considerations in Determining and Disclosing Reasonably Foreseeable Risks

JEREMY SUGARMAN
Johns Hopkins Berman Institute of Bioethics

The Ethics of SOC Research in the Context of the Doctor-Patient Relationship

LEONARD GLANTZ
Boston University School of Public Health

Communicating Reasonably Foreseeable Risks to Research Participants

RUTH MACKLIN
Albert Einstein College of Medicine

COMBINED PANEL

Panelists:
- Charles Weijer, University of Western Ontario
- Jeremy Sugarman, Johns Hopkins Berman Institute of Bioethics
- Leonard Glantz, Boston University
- Ruth Macklin, Albert Einstein College of Medicine
- Don Brunnquell, Children’s Hospitals and Clinics of Minnesota
- Rebecca Dresser, Washington University of St. Louis
- Cindy Geoghegan, Patient and Partners LLC
- Jon Tyson, University of Texas Health Science Center at Houston

Panel Objectives:
- Address the following discussion questions (45 min)
  - What evidentiary standards or criteria are used to determine if a risk is reasonably foreseeable?
  - When, if ever, should the IRB require disclosure of something that it deems to be only minimal risk? What standards should guide these IRB determinations?
o Is there a difference between what a patient considers to be reasonably foreseeable and what medical professionals or researchers might consider reasonably foreseeable?
o What difference (if any) does this make in communicating risks to the patient or study participant? What do patients want to know?
o If any of your answers depends on the specifics of the intervention or type of patient, please elaborate.
  • Discuss relevant areas of the guidance (45 min)

3:35 p.m.  BREAK (15 min)

3:50 p.m.  PUBLIC COMMENT (20 min)
  • Members of the public are invited to sign up to provide comments geared toward the session topic.

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<td>• Collaboratory Coordinating Center (Duke University and Johns Hopkins University) – Kevin Weinfurt</td>
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DAY TWO: December 3, 2014

8:00 a.m. Day Two Opening and Day One Recap

Planning Committee Member: Steven Hyman, Broad Institute of MIT and Harvard

ETHICS OF RESEARCH INVOLVING STANDARD OF CARE INTERVENTIONS: PRELIMINARY FINDINGS

8:05 a.m. Presentation of Preliminary Findings from Ongoing Ethics Studies (40 min)

Session Chair: Robert Califf

- UH3 Project: Time to Reduce Mortality in End-Stage Renal Disease (TiME) (University of Pennsylvania) – Scott Halpern
- ABATE (Active Bathing to Eliminate Infection) Trial Supplement (University of California, Irvine) – Sheila Fireman

SESSION III: FRAMING RISKS OF STANDARD OF CARE INTERVENTIONS – WHAT SHOULD THE CONSENT FORM SAY?

Session Objectives:
- Outline and discuss differences associated with receiving standard of care interventions in a clinical versus a research setting.
  - Discuss whether (and if so, how) the risks and potential benefits of standard of care interventions differ depending on whether they are received in a purely therapeutic clinical context or in a research trial.
  - Consider how risk and potential benefit of standard of care interventions are communicated to patients in clinical practice versus the research setting and how these differences might affect the consent process.
Discuss implications for the review, conduct, and oversight of research studying standard of care interventions.

- Discuss what should be considered risks of research.

8:45 a.m.  **Overview of Session Objectives (5 min)**

**Session Chairs:** Celia Fisher and Marjorie Speers

8:50 a.m.  **Session Presentations**

**Distinguishing Risks of Research from Risks in Therapeutic Clinical Practice**

**ANDY BERTOLATUS**  
University of Iowa

**Ethical Considerations for Communicating Risks of Standard of Care Research**

**JOHN LANTOS**  
Children’s Mercy Bioethics Center

**LEWIS LEAVITT**  
University of Wisconsin-Madison

**Implications for the Research Enterprise**

**ANN BONHAM**  
Association of American Medical Colleges

9:50 a.m.  **COMBINED PANEL**

**Panelists:**

- Andy Bertolatus, University of Iowa
- John Lantos, Children’s Mercy Bioethics Center
- Lewis Leavitt, University of Wisconsin-Madison
- Ann Bonham, Association of American Medical Colleges
- Robert Califf, Duke University
- Valerie Castle, University of Michigan
- Keith Fargo, Alzheimer’s Association
- Edward McCabe, March of Dimes Foundation
- Richard Platt, Harvard Medical School
Panel Objectives:
- Address the following discussion questions (45 min)
  - What are the principles, standards, or guidelines governing disclosure of risks among standard of care interventions in the clinical practice and research setting?
  - Is or should the standard for determining when a risk, or an anticipated side effect, ought to be disclosed the same between research and clinical practice? If not, how do or should they differ?
  - Are risks to a study participant receiving a standard of care intervention in a research setting different compared to a patient receiving a standard of care intervention in a clinical setting? If so, why?
  - How are differences (or similarities) in risk between the clinical and research setting effectively communicated to research participants during the informed consent process? Discuss how this would vary depending on the type patient, severity of disease or illness, and intervention.
  - How do inherent differences in risk and expectations between the clinical and research setting inform us about the review, conduct, and oversight of research studies involving standard of care interventions?
- Discuss relevant areas of the guidance (45 min)

11:20 a.m.  **PUBLIC COMMENT** (20 min)
- Members of the public are invited to sign up to provide comments geared toward the session topic.

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**SESSION IV: CONCLUDING DISCUSSION**

Session Objectives:
- Discuss main points from the workshop.
- Describe key gaps in understanding and explore how best to address those gaps.

11:40 a.m.  **Randomization of Participants**

*Session I Chairs: Steven Hyman and Gregory Simon*

11:50 p.m.  **Criteria for Determining Reasonably Foreseeable Risk**

*Session II Chairs: R. Alta Charo and Clay Johnston*

12:00 p.m.  **Risks of Clinical Interventions and Research within the Standard of Care**

*Session III Chairs: Celia Fisher and Marjorie Speers*

12:10 p.m.  **Discussion with Audience and Wrap-up**

12:30 p.m.  **ADJOURN**