Keynote Address
Addressing the Ethical and Regulatory Issues in Pragmatic Clinical Trials

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Disclosure

- I co-chair the Ethics and Regulatory Core for the NIH Health Care Systems Research Collaboratory and co-led the Ethics and Regulatory Task Force for PCORNet
- I receive(d) salary/grant support through Johns Hopkins University for this work
- The views expressed here are my own and do not necessarily reflect the views of the sponsors, the Collaboratory or PCORNet
Types of Trials

• Explanatory
  – “primarily designed to determine the effects of an intervention under ideal circumstances”

• Pragmatic
  – “primarily designed to determine the effects of an intervention under the usual conditions in which it will be applied”

Attributes of PCTs

1) an intent to inform decision-makers (patients, clinicians, administrators, and policy makers), as opposed to elucidating a biological or social mechanism;

2) an intent to enroll a population relevant to the decision in practice and representative of the patients/populations and clinical settings for whom the decision is relevant;

3) a focus on outcomes of relevance to patients and clinicians; and

4) either an intent to

   (a) streamline unnecessary procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial or

   (b) measure a broad range of outcomes.

Background Conditions

• Broad moral claim to obtain evidence to improve clinical practice since most decisions are now made without reliable evidence to know which choices optimize health

• Technology permits conducting large scale research and cohort finding for rare diseases and special populations, often with minimal incremental risks and burdens and less cost
NIH Health Care Systems Research Collaboratory

• Pragmatic trial design
• Electronic health record as core data collection instrument
• At least 2 integrated health systems collaborating
• 10 demonstration projects
NIH Health Care Systems Research Collaboratory

[Map of the United States with various markers indicating project locations and a legend explaining the markers']
An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics

BY RUTH R. FADEN, NANCY E. KASS, STEVEN N. GOODMAN, PETER PRONOVOYST, SEAN TUNIS, AND TOM L. BEAUCHAMP
Emerging Ethics Issues

- Ethics and regulatory issues in the Collaboratory
- SUPPORT

#1 Consent

• Ethics
  – Traditional approaches MAY be inappropriate and undermine trial integrity
  – Limited data on alternative approaches
  – Research that waives consent can still raise ethical questions, such as privacy

• Regulatory
  – Reluctance to approve alternative approaches
  – Usually requires ‘minimal risk determination’
#2 Risk Determination

• Ethics
  – Debate about what ought to constitute minimal risk

• Regulatory
  – Definitions are subject to interpretation and may not be applied inconsistently in practice
  – Even with a minimal risk determination, the ability to alter consent approach not clear in FDA regulated research
#3 Nature of Interventions

- **Ethics**
  - Interventions directed at systems and clinicians may be evaluated differently than those directed at patients

- **Regulatory**
  - Are differential approaches appropriate?
#4 Identifying Research Participants

- Ethics
  - Direct participants
  - Indirect participants

- Regulatory
  - Who must be considered a “research subject”?
  - What should be done to protect “indirect participants”?
#5 FDA Regulated Products

- **Ethics**
  - Appropriate control of medical products is essential to ensure safety

- **Regulatory**
  - “Off-label” use in research not directed at a new marketing indication results in confusion over regulatory authority
  - FDA regulations typically require written consent
#6 IRBs

**Ethics**
- Effective and efficient oversight that is sensitive to the needs of local populations is essential

**Regulatory**
- Alternative models have been used
  - Central IRBs
  - Reciprocity agreements
  - Shared reviews
- Acceptability for PCTs and CERs is unclear
#7 Research and QI

• Ethics
  – Distinguishing research and QI can be difficult or impossible
  – Regardless, these activities ought to be well conducted and overseen
  – It is inappropriate to label research as QI simply to evade IRB oversight

• Regulatory
  – Appropriate systems should be in place to review such activities
#8 Vulnerable Subjects

- **Ethics**
  - All research participants require appropriate protections

- **Regulatory**
  - Current regulations provide “additional protections” for those deemed vulnerable that may inadvertently undermine PCTs/CER
  - Pathway to protect vulnerable subjects who may be part of clusters is needed
#9 Data Monitoring

• Ethics
  – Interim data review should be conducted as appropriate to ensure the safety and welfare of those in the trial as well as those not in the trial
  – Interim review can help ensure trial integrity
  – Some research models are not designed to conduct interim review, calling for the need for new approaches
  – Balance of data availability and research participants’ protection needs to be struck

• Regulatory
  – Data monitoring plans need to be developed and be consistent with sponsors’ requirements
#10 Gatekeepers

• Ethics
  – Authority, legitimacy, conflicts

• Regulatory
  – Relevant policies and requirements may be unclear
#11 Privacy

• Ethics
  – Rights and interests in controlling personal information

• Regulatory
  – Potential barriers to implementation of large scale research endeavors
March 7, 2013

Richard B. Marchese, Ph.D.,
V.P. for Research & Economic Development
University of Alabama at Birmingham
AB 7205
200 20th Street South
Birmingham, AL 35294-0197

RE: Human Research Protections under Federalwide Assurance (FWA) 5960

Research Project: The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)
Principal Investigator: Dr. Waldemar A. Carlo
HHS Protocol Number: 2018HD042216

Dear Dr. Marchese:

Thank you for your response to our July 18, 2011 letter and subsequent emails regarding our request that your institutions evaluate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) and our subsequent questions and concerns regarding the above-referenced research.

The SUPPORT study was a randomized multi-site study conducted at approximately twenty-two sites and reviewed by at least twenty-three institutional review boards (IRBs). Approximately 1,200 infants were enrolled in this study from 2004 to 2009. The study was designed to 1) learn more about treatment with continuous positive airway pressure (CPAP) which is positive pressure applied with a face mask to help keep the lungs inflated, and 2) to learn the appropriate levels of oxygen saturation in extremely low birth weight infants by comparing a lower versus a higher range of levels of oxygen saturation in such infants. The University of Alabama, Birmingham (UAB) was the lead site for the portion of the study...
Regulatory Criticism of SUPPORT

• “...the informed consent document for this trial failed to adequately inform parents of the reasonably foreseeable risks and discomforts of research participation”
  – “excess risks” of being in the low oxygen arm
  – “excess risks” of being in the high oxygen arm

http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf

Slide courtesy of Steven Joffe, MD, MPH
Study of Babies Did Not Disclose Risks, U.S. Finds

By SABRINA TAVERNESE

Study of premature babies with Children’s Mercy input sparks debate

Parents Not Informed Premature Babies at Risk in Study

Slide courtesy of Steven Joffe, MD, MPH
Alternative Bioethical Views

The OHRP and SUPPORT

The OHRP and SUPPORT — Another View
Public Hearing

Public Meeting August 28, 2013

Public Meeting Transcript
A transcript for the meeting has been posted. View transcript here or in PDF format (PDF - 940 KB). OHRP staff created this transcript from the video captions by correcting transcription errors and identifying the speakers. The caption text accompanying each video is unedited.

August 26, 2013 – Full Meeting Agenda
A full agenda for the August 28, 2013 public meeting has been added to the docket, and is available at this page of the docket.

August 21, 2013 - Information on viewing the August 28, 2013 HHS Public Meeting on Protections of Human Subjects and Research Studying Standard of Care Interventions
For those who cannot attend the August 28, 2013 HHS Public Meeting on the Protections of Human Subjects and Research Studying Standard of Care Interventions, HHS is providing an option to view the public meeting via live streaming technology. To view the HHS public meeting live on August 28, 2013, go to the HHS live streaming site at: www.HHS.gov/live, then hit the "Click to Play" arrow.

On August 16, 2013, HHS added to the docket a basic agenda for the meeting. The basic agenda is available in PDF or Microsoft Word format at this page of the docket.

In a Federal Register notice on June 26, 2013 (PDF - 107 KB), HHS announced a public meeting to be held on August 28, 2013, to seek public input and comment on how certain provisions of the Federal policy for the protection of human subjects should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context.

http://www.hhs.gov/ohrp/newsroom/rfc/Public%20Meeting%20August%2028,%202013/aug28public.html
**Meeting**

**Ethical Review and Oversight Issues in Research Involving Standard of Care Interventions: A Workshop**

**When:** December 2, 2014 - December 3, 2014 (8:30 AM Eastern)

**Where:** National Academy of Sciences Building (Lecture Room) • 2101 Constitution Avenue, NW, Washington, DC 20418

**Topics:** Biomedical and Health Research, Public Health

**Activity:** Ethical Review and Oversight Issues in Research Involving Standard of Care Interventions: A Workshop

**Board:** Board on Health Sciences Policy

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**Other Meeting Resources**

- Agenda
- Videos
- Presentations

**Workshop in Brief**

Standard of Care - Workshop in Brief

**Committee Information**

- Committee Roster
Major Areas of Controversy

• Consent
• Risks and benefits
• Standard of care
EXPLORING THE ETHICAL AND REGULATORY ISSUES IN PRAGMATIC CLINICAL TRIALS
LEADING A SERIES OF 3 ARTICLES ON DIFFERENT ASPECTS OF THIS TOPIC

COLUMN
Clinician Trialist Rounds 2B: When RCT Participants are Lost to Follow-Up: Part I. Why Even a Few Can Matter
MD Marsh, MD Drewes, and Dr. Sackett

TRIBUTE
An Interview with David Sackett
MR Agnolet and RN Goodnow

Full contents are listed on the back cover
Clinical Trials Special Series
Guest Editors: Jeremy Sugarman and Robert Califf

- Informed consent
- Defining minimal risk
- Data monitoring
- Research/quality improvement distinction
- Vulnerable subjects
- Identifying direct and indirect subjects
- Gatekeepers
- IRB harmonization
- FDA-regulated products
- Nature of intervention
- Privacy

http://ctj.sagepub.com/content/early/recent
Workshop Topics
Lessons Learned in the Collaboratory

- Informed consent
- Defining minimal risk
- IRB harmonization
- Data monitoring
- Privacy
- Vulnerable subjects