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"

Thorpe KE, et al. *J Clin Epidem* 2009; 62: 464-475

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.

Califf RM, Sugarman J. *Clin Trials* 2015.

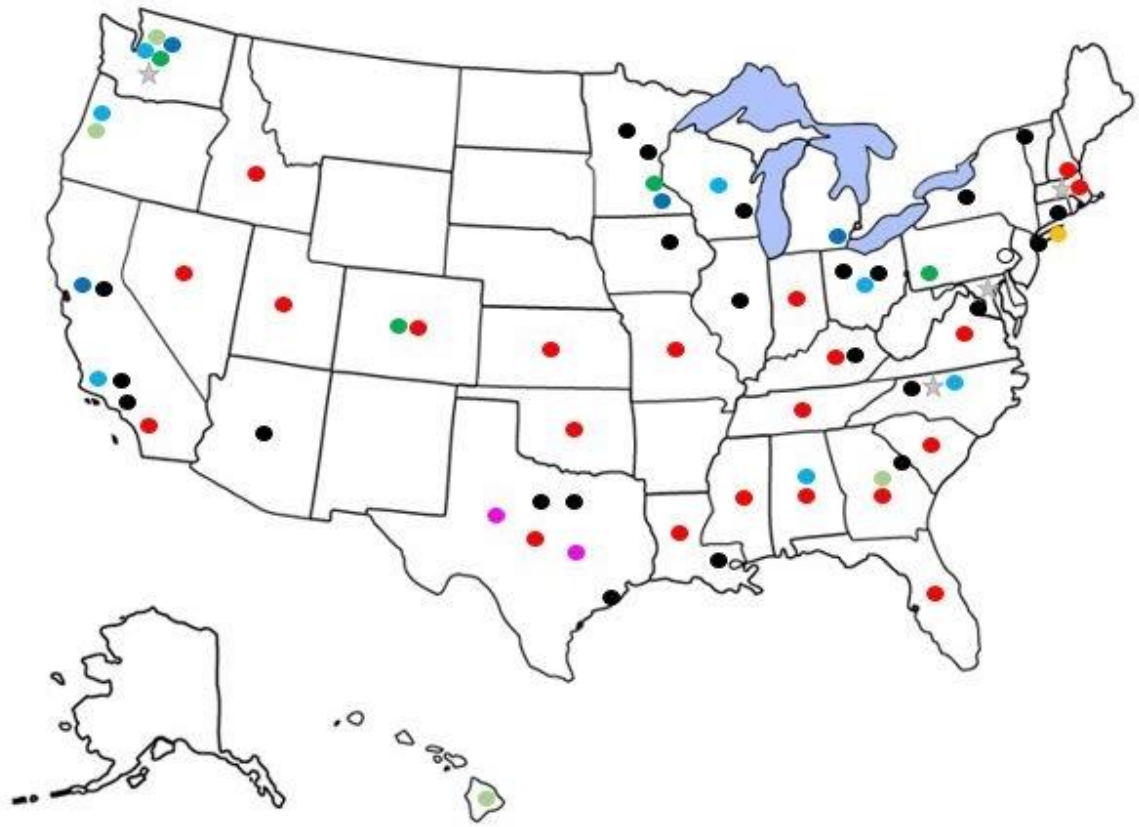
Background Conditions

- 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



- Collaboratory Coordinating Center
- LIRE – Lumbar Image Reporting and Epidemiology
- SPOT – Suicide Prevention Outreach Trial
- TSOS – Trauma Survivors Outcomes and Support.
- TiME – Time to Reduce Mortality in End-Stage Renal Disease
- STOP CRC – Stop Colorectal Cancer in Priority Populations
- PPACT – Collaborative care for Chronic Pain
- PROVEN– Pragmatic Trial for PTSD and Comorbidity
- ABATE – Active Bathing to Eliminate Infection
- ICD-Pieces – Improving Chronic Disease Management

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 PRONOVOST, SEAN TUNIS, AND TOM L. BEAUCHAMP

Emerging Ethics Issues

- Ethics and regulatory issues in the Collaboratory
- SUPPORT

JAMA®

The Journal of the American Medical Association

Sugarman J, Califf RM. Ethics and regulatory complexities for pragmatic clinical trials. *JAMA* 2014; 311: 2381-2382.

Anderson M, Califf R, Sugarman J, for the NIH Health Care Systems Research Collaboratory Cluster Randomized Trial Workshop. Ethical and regulatory issues of pragmatic cluster randomized trials in contemporary health systems. *Clin Trials* 2015; 12: 276-286.

#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

[This letter reflects the removal of an addressee that was not engaged in this human subjects research and replaces the previously issued determination letter (dated February 8, 2013).]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of the Assistant Secretary for Health

Office for Human Research Protections
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Rockville, Maryland 20852

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E-mail: Lica.Buchanan@HHS.gov

March 7, 2013

Richard B. Marchase, Ph.D.
V.P. for Research & Economic Development
University of Alabama at Birmingham
AB 720E
701 20th Street South
Birmingham, AL 35294-0107

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:	2U10HD034216

Dear Dr. Marchase:

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.

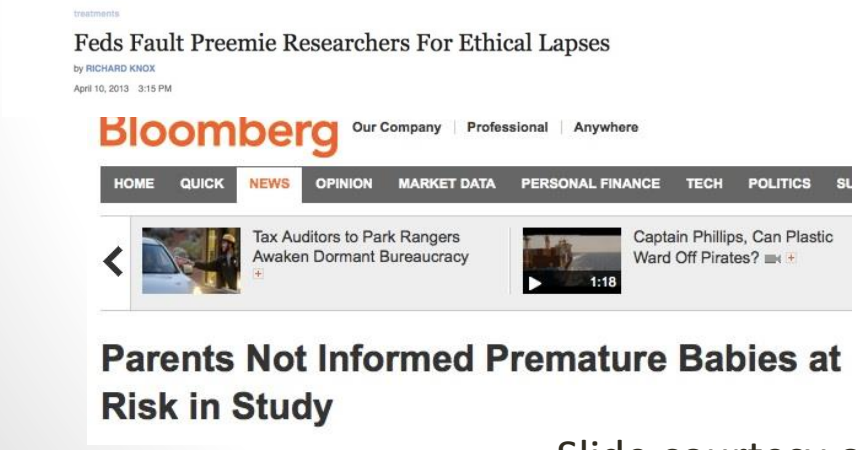
The SUPPORT study was a randomized multi-site study conducted at approximately twenty-two sites and reviewed by at least twenty-three institutional review boards (IRBs). Approximately 1,300 infants were enrolled in this study from 2004 to 2009. The study was designed to 1) learn more about treatment 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



Rethinking Clinical Trials

Slide courtesy of Steven Joffe, MD, MPH

Alternative Bioethical Views

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

The OHRP and SUPPORT

The NEW ENGLAND JOURNAL of MEDICINE

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The OHRP and SUPPORT — Another View

Public Hearing

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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

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Meeting

Print

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

Other Meeting Resources

- Agenda
- Videos
- Presentations

Workshop in Brief

Standard of Care - Workshop in Brief

Committee Information

- Committee Roster

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Major Areas of Controversy

- Consent
- Risks and benefits
- Standard of care

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CLINICAL TRIALS

Journal of the Society for Clinical Trials

EXPLORING THE ETHICAL AND REGULATORY ISSUES IN PRAGMATIC CLINICAL TRIALS LEADING A SERIES OF 12 ARTICLES ON DIFFERENT ASPECTS OF THIS TOPIC

COLUMN

Clinician Trialist Rounds 28: When RCT Participants are Lost to Follow-Up. Part I: Why Even a Few Can Matter
M Walsh, PJ Devereaux and DL Sackett

TRIBUTE

An Interview with David Sackett
RB Haynes and SN Goodman

Full contents are listed on the back cover

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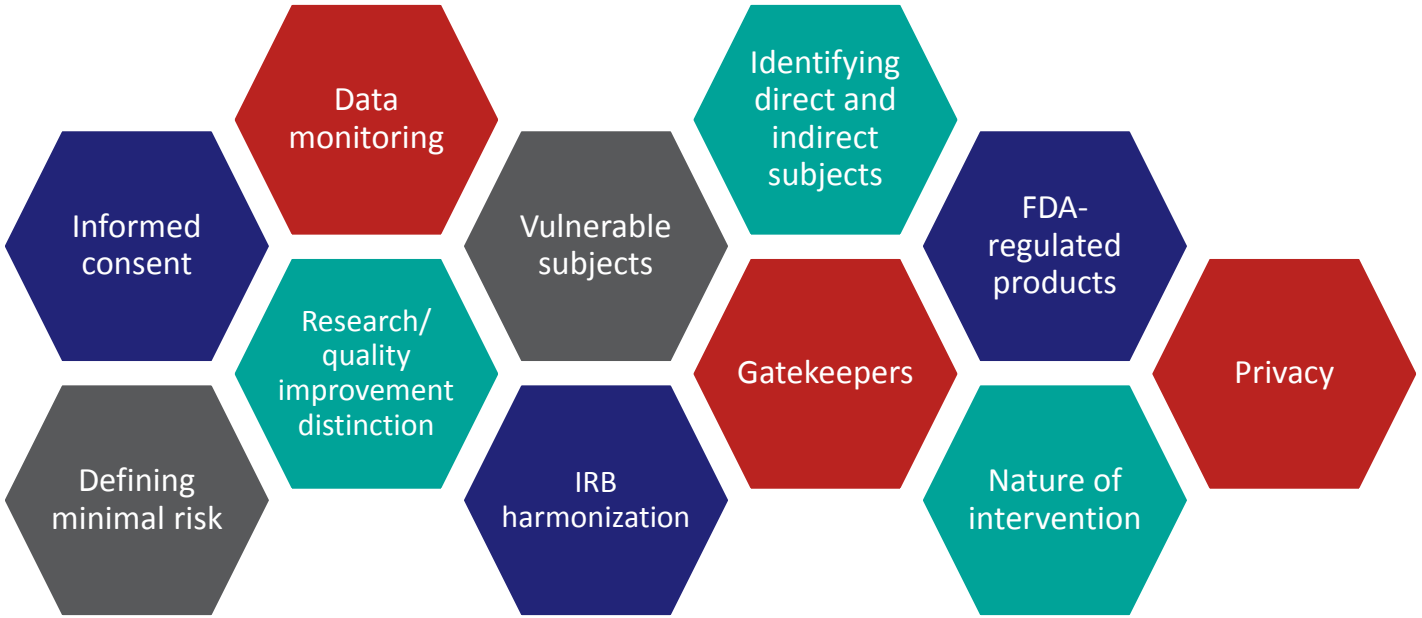
Clinical Trials Special Series

Guest Editors: Jeremy Sugarman and Robert Califf



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Workshop Topics
Lessons Learned in the Collaboratory