

## Rethinking Research/Rethinking Research Ethics: Considerations for Pragmatic Clinical Trials

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## Disclosure

- I am a member of Merck KGaA's Bioethics Advisory Panel and Stem Cell Research Oversight Committee; and a member of IQVIA's (formerly Quintiles) Ethics Advisory Panel
- I co-chair the Ethics and Regulatory Core for the NIH Health Care Systems Research Collaboratory and co-lead 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

## Objective

- Describe some of the key ethical and regulatory challenges associated with pragmatic clinical trials.

## Types of Trials

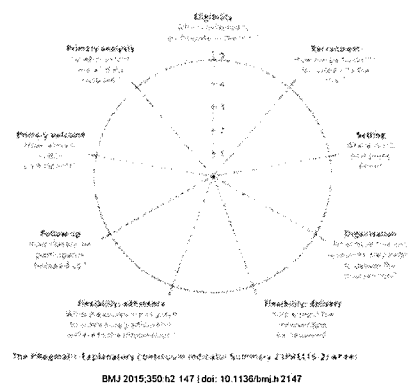
- Explanatory
  - “primarily designed to determine the effects of an intervention under ideal circumstances”
- Pragmatic
  - “primarily designed to determine the effects of an intervention under the usual conditions in which it will be applied”

Thorpe KE, et al. *J Clin Epidemiol* 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.



## Comparative Effectiveness Research

“is the direct comparison of existing health care interventions to determine which work best for which patients and which pose the greatest benefits and harms. The core question of comparative effectiveness research is which treatment works best, for whom, and under what circumstances.”

[http://en.wikipedia.org/wiki/Comparative\\_effectiveness\\_research](http://en.wikipedia.org/wiki/Comparative_effectiveness_research)

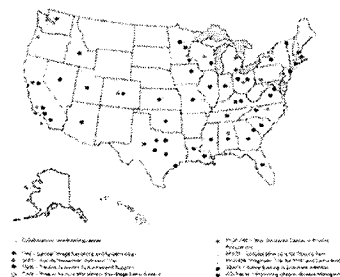
## Background Conditions

- There is a 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 + 5 new projects approved for a planning phase

NIH Health Care Systems Research  
Collaboratory



An Ethics Framework for a Learning Health Care System: *A Departure from Traditional Research Ethics and Clinical Ethics*

[illegible]

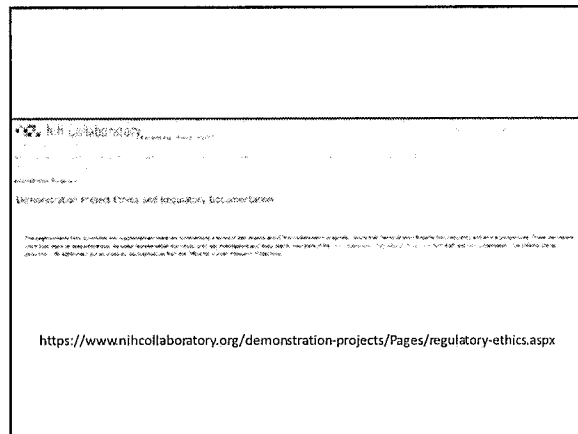
Hastings Cent Rep 2013 Jan/Feb:S16

## Emerging Ethics Issues

- Ethics and regulatory issues in the Collaboratory
- SUPPORT

## Ethics and Regulatory Issues in the Collaboratory

- Multi-stakeholder conversations at the planning stage convened by the Ethics & Regulatory Core
  - Investigators and research teams
  - Sponsors
  - IRBs
  - Regulators
- Minutes reviewed and posted
- Updates following project implementation



**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.

**CLINICAL  
TRIALS**  
A JOURNAL OF THE  
AMERICAN SOCIETY OF  
CLINICAL TRIALISTS

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'

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## #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

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## #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?

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#### #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”?

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#### #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

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#### #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

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#### #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

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#### #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

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#### #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

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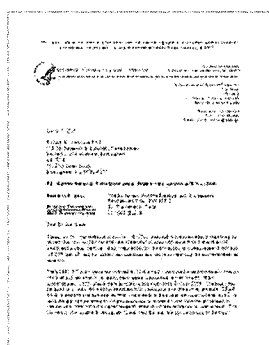
## #10 Gatekeepers

- Ethics
  - Authority, legitimacy, conflicts
- Regulatory
  - Relevant policies and requirements may be unclear

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## [#11 Privacy]

- Ethics
  - Rights and interests in controlling personal information
- Regulatory
  - Potential barriers to implementation of large scale research endeavors

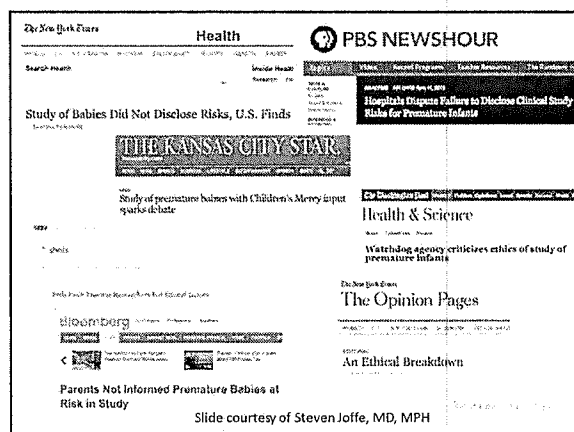


## Regulatory Criticism of SUPPORT

- “...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\\_lets/YR13/mar13a.pdf](http://www.hhs.gov/ohrp/detrm_lets/YR13/mar13a.pdf)

Slide courtesy of Steven Joffe, MD, MPH



Slide courtesy of Steven Joffe, MD, MPH

## Alternative Bioethical Views

CORRESPONDENCE



The OHRP and SUPPORT

THE OHRP AND SUPPORT: ANOTHER VIEW

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The OHRP and SUPPORT — Another View

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## Meeting

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

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#### Other Meeting Activities

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- Consent
- Risks and benefits
- Standard of care



**SCT**

A cluster of ten interconnected hexagons, each containing a key concept in research ethics. The concepts are: Data monitoring, Identifying direct and indirect subjects, FDA-regulated products, Privacy, Nature of intervention, Gatekeepers, IRB harmonization, Defining minimal risk, Research/quality improvement distinction, and Informed consent.

<http://ctj.sagepub.com/content/early/recent>

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### Concluding Comments

- Addressing the ethical and regulatory challenges of PCTs is surprisingly complex
- The well-rehearsed habit of 'adding protections' in research ethics *may not* be actually be providing needed protections and may inadvertently stymie important research efforts
- Additional data and deliberation should help inform the development of appropriate policies and procedures
  - Supplement to *AJOB Empirical Bioethics*
  - Living Textbook