



Health Care Systems Research Collaboratory

# Ethics and Regulatory Complexities for Pragmatic Clinical Trials

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# EXCERPTS from RECENT GRAND ROUNDS



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# THE ETHICS AND REGULATORY LANDSCAPE: IS A MASSIVE PUBLIC CAMPAIGN NEEDED?

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# Do We have a Problem?

## ARGUMENT FOR YES

We lack evidence for most health and healthcare decisions

Ignorance in medical practice is dangerous

“Research exceptionalism” is paralyzing learning

## ARGUMENT FOR NO

We have a history and a rationale for ethical oversight of research to prevent harm to research subjects

Practice is governed by the “doctor-patient” relationship

The system is working

# Office of Human Research Protections

- Questions raised about comparison of accepted approaches to clinical care in practice
- Particular concerns about consent
  - When is it necessary?
  - When can it be modified?
  - Is randomization itself a risk?
- A diversity of opinions expressed at a public hearing at HHS
- Summary document from the meeting is pending and expected any day

# Federal Research Policy (HHS)

- The Federal Policy for the Protection of Human Subjects or the “Common Rule” was published in 1991 and codified in separate regulations by 15 Federal departments and agencies, as listed below.
  - 45 CFR part 46, include four subparts:
    - subpart A, also known as the Federal Policy or the “Common Rule”;
    - subpart B, additional protections for pregnant women, human fetuses, and neonates;
    - subpart C, additional protections for prisoners;
    - and subpart D, additional protections for children.
- <http://www.hhs.gov/ohrp/humansubjects/commonrule/>

# The Common Rule

- Although they have not issued the Common Rule in regulations, three other departments and agencies comply with all subparts of 45 CFR part 46. These include:
  - The Central Intelligence Agency, by executive order, must comply with all subparts of 45 CFR Part 46. (Executive Order 12333, paragraph 2.10)
  - The Department of Homeland Security, created after issuance of the Common Rule, has chosen to apply all subparts of 45 CFR part 46 to its human research activities. (6 U.S.C. section 112)
  - The Social Security Administration was separated from HHS in 1994 and, absent action by the Administrator, must apply all regulations that applied to SSA before the separation. (42 U.S.C. section 901)
    - <http://www.hhs.gov/ohrp/humansubjects/commonrule/>

ANPRM for Revision to Common Rule  
**HHS Announces Proposal to Improve Rules  
Protecting Human Research Subjects**  
*Changes under consideration would ensure  
the highest standards of protections for  
human subjects involved in research, while  
enhancing effectiveness of oversight*

July 22<sup>nd</sup>, 2011; still waiting!





# Summary

- Our research system is only answering a fraction of the questions that are critical to inform practice and health decisions by patients
- The system is complex, highly regulated and resistant to change
- A combination of new guidances and substantial empirical data will influence the landscape for the foreseeable future, but there is no assurance that these different inputs will be mutually reinforcing
- The clinical research community is not in a good position to advocate for changes that would increase knowledge because of accusations of self serving behavior
- **A strong and well-informed patient voice is needed!**

# THE CREDIBLE HULK



You wouldn't like me  
when I'm angry  
because I always  
back up my rage  
with facts and  
documented  
sources.



# Time to Take Action!

- Unacceptable:
  - Lack of evidence for accepted approaches
  - Disparities
  - Lack of responsiveness to the shifting regulatory foundation
  - Lack of engagement on part of the stakeholders/public

# Let's Get Organized!

- Large and well coordinated advocacy effort
- Deep disease specific advocacy expertise has been honed for 50 years
- Issues are too big for one network or org
- Need collaboration to awaken public: ultimately benefiting all who suffer, or who will suffer
- Harness power of networks at same time we create PCORnet and other networks.
- No network will succeed without equal power of advocacy



# What do we have to lose?

# Everything.



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# Ethics and Regulatory Complexities for Pragmatic Clinical Trials

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Sugarman J, Califf RM. *JAMA* 2014; 311: 2381-2382.

Rethinking Clinical Trials

# The Need for Data

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

# Background Conditions

- Two broad areas
  - Data
  - Clinical research operations
- 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





# Potential Barriers

- Such research is associated with ethical and regulatory complexities
- Well-intentioned research in the setting of usual care may encounter controversy (eg, SUPPORT)
- Ethics rationale for alternative approaches are not universally accepted (ie, there are differences of opinion)
- Regulatory pathways are not always clear

# #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'
    - Pathways for modified consent unclear

# #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?
  - Draft SACHRP Guidance publicly available for comment

# #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

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# #10 Gatekeepers

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

# #11 Privacy

- Ethics
  - Autonomy interest in controlling personal information
  - Welfare interest in protection from harm
    - Stigma
    - Discrimination
- Regulatory
  - HIPAA
  - Other mandates



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# Ethics and Regulatory Papers

# Writing Teams

- **Definition of minimal risk**
  - **Co-Lead** – Robert Califf, MD
  - **Co-Lead**-- John Lantos, MD
  - Rosemary Madigan, RN, MS, MPH
  - Sarita Wahba, MSPH, MS
  - Dave Wendler, MA, PhD
- **Research/QI distinction in practice**
  - **Lead** –Jonathan Finkelstein, MD, MPH
  - Andrew Brickman, PhD
  - Daniel Davis, PhD
  - Sarah Greene, MPH
  - Daniel Ford, MD, MPH
  - Sarah Pallin, MPH
  - Mark Pletcher, MD
- **Waiver or modification of consent/Alternate models of notification**
  - **Lead** – Ross McKinney, MD
  - Laura Beskow, PhD
  - Jessica Burris
  - Clara Filice, MD, MPH, MHS
  - Daniel Ford, MD, MPH
  - John Lantos, MD
  - Bray Patrick-Lake, MS
  - Mark Pletcher, MD
  - Brian Rath, Esq
  - Hollie Schmidt, MS
  - Kevin Weinfurt, PhD

# Writing Teams

- **Data monitoring in PCTs**
  - **Lead** – Susan Ellenberg, PhD
  - Richard Culbertson, PhD
  - Dan Gillen, PhD
  - Jim Sabin, MD
  - Jeremy Sugarman, MD, MPH, MA
- **Achieving IRBs harmonization and efficiency in PCTs**
  - **Lead** - John Lantos, MD
  - Jeremy Corsmo, MPH
  - Rachael Fleurence, PhD
  - Stephanie Gaudreau
  - Raffaella Hart, CIP
  - Pearl O'Rourke, MD
  - Bray Patrick-Lake, MS
  - Todd Rice, MD

- **Vulnerable subjects in CRTs**
  - **Lead** – Mary Jane Welch, DNP, APRN, BC, CIP
  - James Fischer, PHARM.D., FCCP
  - Peg Hill-Callahan
  - Rachel Lally, MPH
  - Amanda Terry, MA, CRA
  - Roberta Tovey, PhD

# Writing Teams

- **Gatekeepers in PCTs**
  - **Lead** - Danielle Whicher, PHD, MHS
  - Robert Califf, MD
  - Kelly Clayton, MPH
  - Susan Surovec
  - Amanda Terry, MD, CRA
- **Identifying direct and indirect subjects/participants in CRTs/Risk and benefit balance assessment**
  - **Lead – Jaye Bea Smalley**
  - Kelly Edwards, PhD, MA
  - Megan Gauvey-Kern
  - Debbe McCall, MBA
  - Carl Stepnowsky, PhD
- **FDA regulated products and PCTs**
  - **Lead** – Monique Anderson, MD
  - Denise Cifelli, MS
  - Sheila Fireman, MA, JD
  - Nancy Stade, JD



# Writing Teams

- **Ethics and the nature of interventions in PCTs (e.g., physician vs. patient)**
  - **Lead – Needed**
  - Zia Agha, MD
  - Kathryn James, PA, MPH
  - Lindsay Kindler, PhD, RN, CNS
  - C. Eglar Rabinovich, MD, MPH
  - Carol Somkin, PhD
- **Privacy**
  - **Lead** – Deven McGraw, JD
  - Sarah Greene, MPH
  - Caroline Miner, MA
  - Jeremy Sugarman, MD, MPH, MA
  - Mary Jane Welch, DNP, APRN, BC, CIP
- **Plain Language Product Reviewers**
  - Geraldine Bliss, MS
  - Mary Elkins Melton
  - Dena Rifkin, MD, MS
- **Internal/Independent Reviewer**
  - Arthur Caplan, PhD

# Proposed Timeline

- 10/1/14 - Outlines due
- 12/1/14 - First drafts due; Internal editorial review (Califf, Caplan and Sugarman)
- 1/5/15-1/9/15 - Writing workshop
- 1/12/15 - Manuscripts out for external peer review
- 3/15/15 - Revised manuscripts due; Internal editorial review (Califf and Sugarman)
- 4/1/15- Copy edited versions to *Clinical Trials*



# Jamboree Planned 2<sup>nd</sup> Week in January