

NIH Policy Priorities for Clinical Research

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Federal Demonstration Partnership

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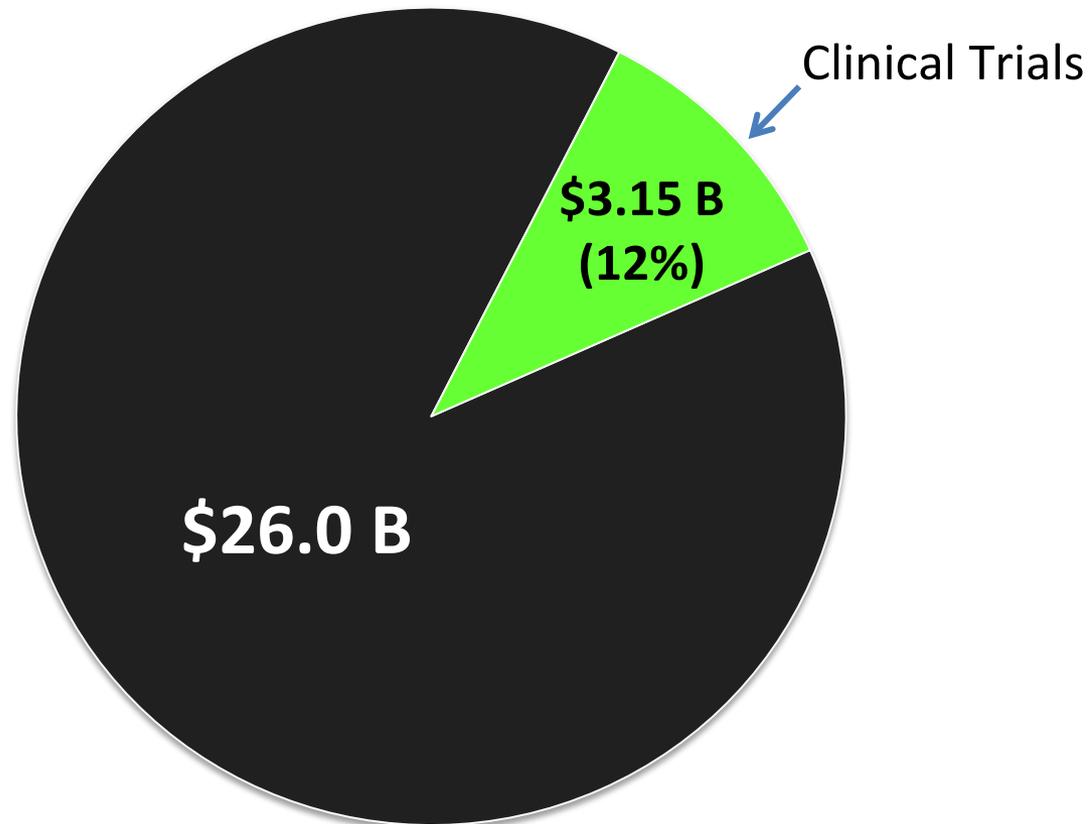
Topics

- ❖ Clinical Trial Results Reporting & Data Sharing
- ❖ Single IRB
- ❖ Standard of Care Research

Clinical Trial Results

NIH Clinical Trials

NIH FY 2013 Budget (\$29.15 billion)



Public Benefits of Clinical Trial Data Sharing

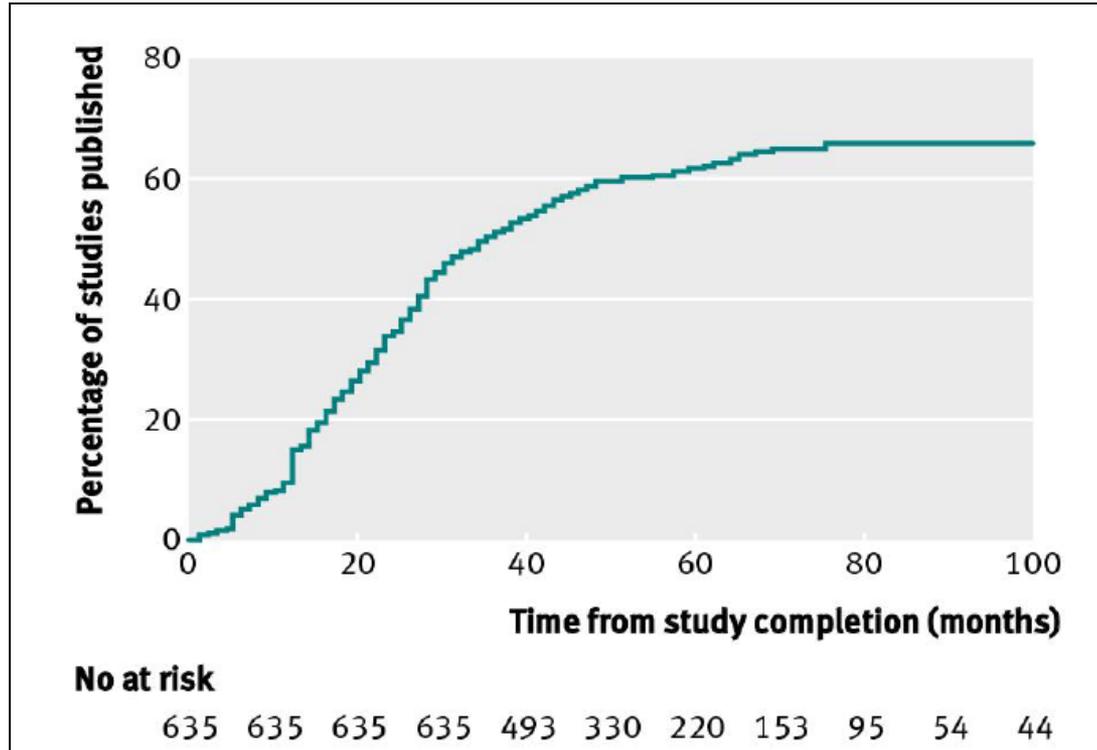
- Inform future research and research funding decisions
- Mitigate bias (e.g., non publication of results, especially negative results)
- Prevent duplication of unsafe trials
- Meet ethical obligation to human subjects (i.e., that results inform science)
- Increase access to data about marketed products

All contribute to public trust in clinical research

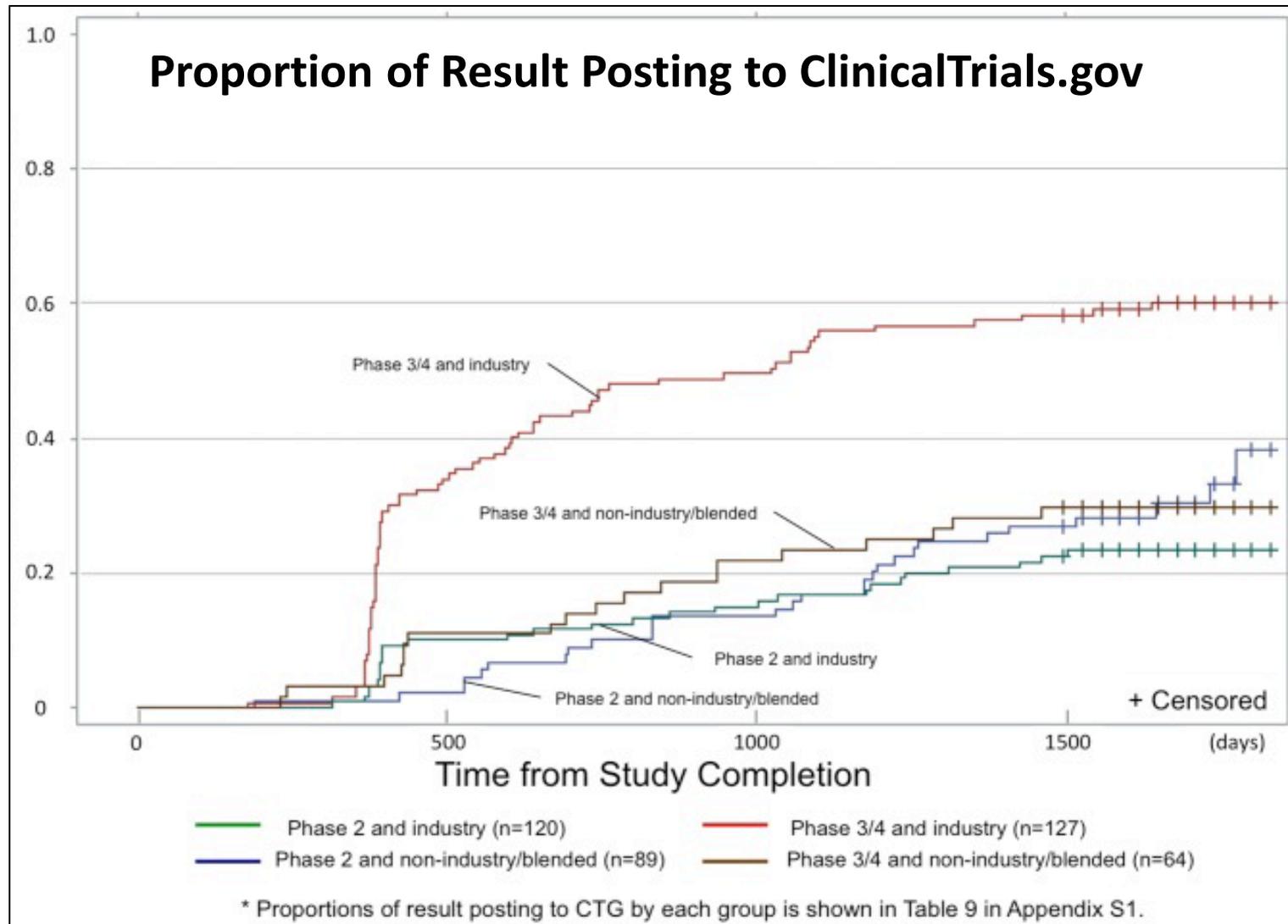
Yet...Poor Publication Rates of Clinical Trial Results

NIH-Funded trials published within 100 months of completion

- Less than 50% are published within 30 months of completion
- Our own data show the same trends



And Dissemination of Results Overall



So, on November 21, 2014...



JAMA The Journal of the
American Medical Association

Opinion

VIEWPOINT

Sharing and Reporting the Results of Clinical Trials

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The principle of data sharing dates to the dawn of scientific discovery—it is how researchers from different disciplines and countries form collaborations, learn from others, identify new scientific opportunities, and work to turn newly discovered information into shared knowledge and practical advances. When research involves human volunteers who agree to participate in clinical trials to test new drugs, devices, or other interventions, this principle of data sharing properly assumes the role of an ethical mandate. These participants are often informed that such research might not benefit them directly, but may affect the lives of others. If the clinical research community fails to share what is learned, allowing data to remain unpublished or unreported, researchers are renegeing on the promise to clinical trial participants, are wasting time and resources, and are jeopardizing public trust.

Across public and private sectors, the United States has increasingly focused on data sharing, including through directives from the White House to ensure that valuable scientific data generated with federal funding are publicly available and useable.¹ As the largest public

be blamed entirely. A recent analysis of 400 clinical studies revealed that 30% had not shared results through publication or through results reporting in ClinicalTrials.gov within 4 years of completion.⁴ This is a serious issue and the proposed rule underscores the intent of NIH to take strong action to promote timely dissemination of clinical trial results.

Without access to complete information about a particular scientific question, including negative or inconclusive data, duplicative studies may be initiated that unnecessarily put patients at risk or expose them to interventions that are known to be ineffective for specific uses. If multiple related studies are conducted but only positive results are reported, publication bias can distort the evidence base. Incomplete knowledge can then be incorporated into clinical guidelines and patient care. However, one of the greatest harms from non-disclosure of results may be the erosion of the trust accorded to researchers by trial participants and, when public funds are used, by taxpayers.

The efforts to make information derived from clinical trials public has been under way for nearly

NIH Requ
NIH-Fund

Notice Num
NOT-OD-15-01

Key Dates

Release Date: Nove

Response Date: Fe

Related Ann

None

Issued by

National Institutes of Health (NIH)

Purpose

Summary

The National Institutes of Health (NIH) is seeking public comments on a draft policy to promote broad and responsible dissemination of information on clinical trials funded by

of

ER

FDAAA Title VIII

- Applies to public & private sector
- Covers trials of FDA-regulated:
 - drugs and biologics (except phase 1)
 - devices (except small feasibility studies)
 - pediatric postmarket surveillance studies of devices required by FDA
- Requires trial registration before 21st day after enrollment begins
- Requires submission of summary results of trials of approved products
- Includes enforcement provisions
 - Notices of non-compliance
 - Withholding of NIH/HHS grant funds
 - Civil monetary penalties up to \$10,000/day (FDA)

Notice of Proposed Rulemaking: *Clinical Trials Registration & Results Submission*

- Clarifies FDAAA's registration and basic results submission requirements
- Proposes to require submission of results of unapproved products
- Asks for comment on whether to require narrative summaries
- Asks for comment on whether to require submission of protocols

FDAAA Compliance Provisions

- FDA authorized to levy monetary penalties
- NIH *must* verify submission of information before releasing any remaining funds for a grant or funds for a future grant
- Grant and progress report forms must certify information has been submitted
- NIH must provide responsible parties with notice of non-compliance
- Non-compliance must be made public through ClinicalTrials.gov
- Considering carrots and sticks to increase compliance – for both extramural and intramural trials



Trial Types *NOT* Covered by FDAAA

- Phase 1 trials of FDA-regulated drugs and biologics
- Small feasibility device studies
- Pediatric postmarket surveillance studies that are not required by FDA
- Trials of interventions that are not regulated by FDA, e.g., behavioral trials, surgical trials
- Observational studies (i.e., where usual/standard of care interventions are assigned by clinician in the course of care)

We need all NIH-funded clinical trials posting results

Number of Clinical Trials Initiated Annually – ACTs and Others

	Total	NIH Funded	Other Federally Funded
ACTs of approved products (FDAAA)	1,850	400	40
ACTs of unapproved products (NPRM)	7,400	900-1200	200
Other Clinical Trials (not ACTs)	9,600	500-650	200

Draft NIH Policy: *Dissemination of NIH-funded Clinical Trial Information*

- Expects registration and results submission to ClinicalTrials.gov for all NIH clinical trials regardless of
 - phase
 - type of intervention
 - whether they are subject to FDAAA
- Same timelines as FDAAA
 - Registration not later than 21 days after enrollment
 - Submission of results one year after the completion date

Clinical Trial Registration & Results Reporting

- ***Notice of Proposed Rulemaking*** on Clinical Trials Registration and Results Submission published for a 90 day comment period in the *Federal Register* on November 21, 2014.
 - Comments to Docket No. NIH-2011-0003 at <http://www.regulations.gov> (NIH staff who wish to comment may not do so in official capacity)
- ***Draft NIH Policy*** on Dissemination of NIH-funded Clinical Trial Information published for a 90-day comment period in the *NIH Guide for Grants and Contracts* on November 19, 2014.
 - Comments to clinicaltrials.disseminationpolicy@mail.nih.gov

**NOTE: In response to requests, we will be extending the comment period by a month.*

More Data Sharing Coming

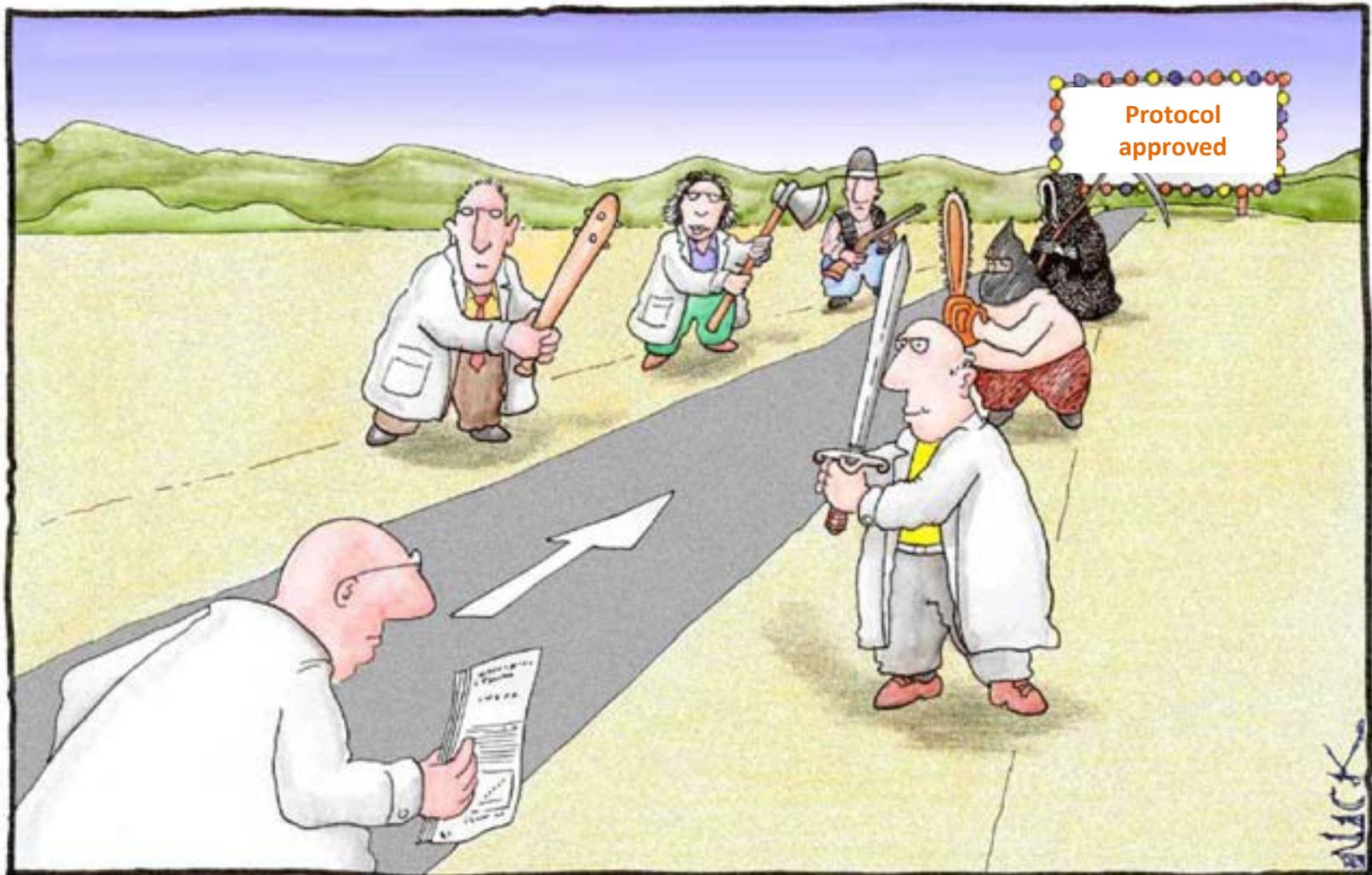
- IOM Report on Strategies for Responsible Sharing of Clinical Trial Data – *public Jan 14th*
 - Recs on clinical trial data sharing, including participant level data
- White House Directives in 2013
 - Open Data Policy – Requires agencies to make administrative and scientific data publicly available
 - Holdren Memo –
 - All science agencies must increase access to federally funded scientific data
 - Require all investigators to develop data management/sharing plans by end of 2015

Data Management Plan Elements

- Investigator commitment to the principle of data sharing
- Types of data expected to be produced
- Standards to be used in collection
- How and when data will be shared (or, why it can't be)
- Tools, including software, needed to enable data access and/or interpretation
- Where needed, provisions for protection/security of data & to address IP issues
- Plans for data archiving and long-term preservation

Single IRB

Multi-site IRB Review: There has GOT to be a better way



NIH Models of Single IRBs

- Extramural Program
 - NCI Central IRB (CIRB)
 - NeuroNEXT
 - StrokeNet
 - Others in development (e.g., CTSAs)
- Intramural Program
 - Undiagnosed Diseases Program
 - PHERRB

Why Move to a Single IRB of Record?

- Multiple IRB review does not appear to enhance protections for participants
- Single IRB review reduces **costs** and **review time**, and increases **consistency**
- Consistent with Common Rule reform mandate (as described in the ANPRM)
- Concept has been tested by NIH and others
- Strong interest in this in Congress (21st Century Cures, etc) -

Why Move to a Single IRB of Record?

Reduces costs

- Cost of multiple IRB review of one study = \$431 – \$799/protocol
- NCI CIRB review = \$91 – \$106

Reduces review time

- NCI CIRB review was 34 days faster than local review
- NeuroNEXT protocol fully approved and enrolling within 56 days³
- Staff spent an average of 6.1 fewer hours on protocols that received CIRB review for a cost saving of \$717

Sources: Wagner, et al, *J Clin Oncol*. 2010 Feb 1;**28**(4):662-6.; Kaufmann, et al, *Acad Med*. 2014 Nov 18

Why Move to a Single IRB of Record?

Increases consistency

Two examples:

- Pediatric protocol, 34 IRBs: 13 approved without changes, 18 conditional approvals, 3 deferred approval
- Observational health services research protocol, 43 IRBs
 - 1 site found the protocol exempt, 10 sites – eligible for expedited review, 31 required full review, 1 site rejected the study as too risky
 - NOTE: took ~4680 hours of staff time over 19 months

Sources: Higgerson, *et al*, *Pediatrics*, 2014 Aug;134(2); Green, *et al*, *Health Serv Res*. 2006 Feb;41(1):214-30

Investigator Preferences

NIH-funded study (2014), human genetics researchers were asked

How important would the following be to facilitating genomic research, on a scale of 1 to 10, where 1 is not at all important and 10 is very important: A single IRB of record for multi-site studies.

- 30% rated single IRB as a 10
- 61% rated as an 8 or higher
- 75% rated as a 7 or higher
- 10% rated as a 4 or lower

Building Evidence to Inform Policy

FY 2014 Bioethics Awards

Central IRBs overseeing multisite studies (2 awards)

- *Using real world decisions to develop a modified central IRB model*

Understand the rationale used when selecting a cIRB, including barriers; evaluating alternative models on key outcomes (e.g. ethical quality, efficiency of review)

- *Central IRBs: Enhanced Protections for Human Research Participants?*

Characterize organizational aspects and procedural features of cIRBs; assess differences between local and central review;

Draft NIH Policy on the Use of a Single IRB for Multi-Site Research

- NIH-funded multi-site studies in U.S.
- Single IRB identified by the applicant; IC has final approval
- Costs of fee-based IRB review will be included in the award as a direct cost
- Exceptions allowed if:
 - A designated IRB is unable to meet the needs of specific populations; or
 - Local IRB review is required by federal, tribal, or state laws or regulations.

Draft NIH Policy on the Use of a Single IRB for Multi-Site Research

- Published in the NIH Guide on December 3, 2014
- 60 day comment period
- We've heard a lot already
 - PRIM&R meeting in Baltimore
 - Conference call with academic representatives organized by AAMC, AAU, APLU, COGR
 - NIH Director's Advisory Committee (ACD) – very supportive
- Support the general concept; concerns about implementation
- We are interested in institutional experience, examples of various models, and ***empirical data*** on central vs local review

Standard of Care Research

SUPPORT

Surfactant, Positive Pressure and Pulse Oximetry Randomized

- DESIGN: 1,316 infants (24-27 wks ga) randomized within standard of care: **85-89%** or **90-95%** oxygen saturation (AAP rec. 85-95)
- STUDY: Carried out at >20 Sites from 2004 – 2009
- QUESTION: Ideal oxygen saturation targets for preterm infants?
- GOAL: Identify the target that would minimize the risk of ROP;
no known increased risk of death within SOC range
- RESULTS:
 - ROP was reduced at lower range
 - Incidence of death increased at lower range;
16.2% to 19.9% (P = 0.04) – **Unexpected**



SUPPORT: OHRP's Position

Surfactant, Positive Pressure and Pulse Oximetry Randomized

- Study involved “substantial risks” that were not disclosed.
- “the level of oxygen being provided to some infants, compared to the level they would have received had they not participated, could increase the risk of brain injury or death.”
- Randomizing to arms both within the standard of care places participants at risk.

“Their position is apparently that informed consent forms need to inform parents not only of known risks and of possible risks, but also of risks that the investigators did not think were possible – even after those risks have been shown not to exist.”

John Lantos, 4/18/13

Hastings Bioethics Forum

SUPPORT: *Divided Community*

And those who don't

Those who agree with OHRP

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE



The OHRP and SUPPORT

TO THE EDITOR: We are a group of scholars and leaders in bioethics and pediatrics with extensive experience that the institutional bodies responsible for reviewing SUPPORT failed to exercise appropriate

NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE



OHRP and SUPPORT — Another View

TO THE EDITOR: We are a group of physicians, bioethicists, and scholars in allied fields who agree with the Office for Human Research Protection from usual clinical care, and that information should have been included in the consent forms. About half the forms indicated that because

NIH weighs in



Building Evidence to Inform Policy

FY 2013 Bioethics Awards

NIH-funded studies on ethical issues surrounding standard of care, FY13

- **U Penn; Laura Dember, Scott Halpern**

Understand how patients value physician autonomy to choose treatment strategies within the standard of care

- **UC Irvine; Susan Huang**

Insight into expected improvements in healthcare (QI) and what constitutes research

- **Duke, Johns Hopkins; Rob Califf, Jeremy Sugarman**

Preferences about research & consent in the setting of usual care

- **U Washington, Stanford; Ben Wilfond, David Magnus**

Understand how patients, general public, IRBs view the ethical implications of randomization within the standard of care

OHRP's Draft Guidance

Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care

Published in the Federal Register on **October 24, 2014** for **60 day comment period** – deadline **extended to January 22nd** following request from patient groups

Addresses four topics:

- What are “standards of care”?
- What are “risks of research” in studies evaluating risks associated with standards of care?
- When is evaluating a risk in a research study considered to be a “purpose” of the research study?
- What are “reasonably foreseeable risks” that must be disclosed to prospective subjects in the informed consent process?

OHRP Guidance says...

(2) the identified risks the research proposes to evaluate as one of the purposes of the study are reasonably foreseeable risks that generally must be disclosed to prospective subjects when seeking their informed consent (45 CFR 46.116(a)(2)).

Does this Work in Real-World Examples?

A study comparing interventions in suicide prevention. Efficacy will be measured by the impact of one or more of these interventions on **suicide attempt and/or suicide death**.

Is it rational to view suicide as a risk of the research?

The Lung Screening Study, randomized 55,000 people who were smokers to receive different screening tests for lung cancer – chest X-ray or low dose CT. Usual practice leaves screening at the discretion of the practitioner and patient, but most patients do not get screened. The outcome measures were either **rates of lung cancer or deaths from lung cancer**.

Is it rational to view death from lung cancer as a research risk of the research?

IOM Workshop

December 2-3, 2014

- NIH commissioned
- Public forum for in-depth discussion of ethical issues in SoC research
 - Distinguishing risks of *the research from risks of treatment*
 - Criteria for identifying reasonably foreseeable risks
 - Is randomization a risk?
 - Role of IRBs in assessing and overseeing SoC research
 - Communication of information to patients
- Widely attended by patient advocates, researchers, bioethicists.
- Webcast available:
<http://www.iom.edu/Activities/Research/StandardofCare/2014-DEC-02.aspx>

Comments & Questions?