The Necessity for Clinical Trials Innovation: Making it Work at the National Heart, Lung, and Blood Institute

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So What’s the Problem?

- Comparing relevant alternatives
- Diverse populations, heterogeneous practices
- Broad range of (relevant) health outcomes
- Limited resources, misaligned missions

Tunis SR et al. JAMA 2003;290:1624-32
With 10 to 15% paylines at some institutes (or even less), the current situation makes grant evaluation nearly impossible and is putting truly excellent laboratories out of business. In the spirit of “never waste a good crisis,” a serious evaluation of many NIH extramural policies and programs is warranted. They include centers and other large collective funding efforts as well as expensive clinical and epidemiological research.
We Did a Serious Evaluation ...

**Publication of Trials Funded by the National Heart, Lung, and Blood Institute**

David Gordon, M.D., Ph.D., Wendy Taddei-Peters, Ph.D., Alice Mascette, M.D., Melissa Antman, Ph.D., Peter G. Kaufmann, Ph.D., and Michael S. Lauer, M.D.

Unadjusted rate ratio, 5.47 (95% CI, 3.74–7.98); P=0.001
Adjusted rate ratio, 2.11 (95% CI, 1.26–3.53); P=0.004

Duration (yr)

- ≥6
- 5–6
- 4–5
- 3–4
- ≤3

No. of Trials

- <150
- 150–249
- 250–499
- 500–999
- 1000–4999
- 5000–9999
- >10,000

Cumulative Publication Rate

- Clinical end points
- Surrogate end points

No. at Risk

- Surrogate end points: 199, 158, 110, 67, 40, 24, 16
- Clinical end points: 45, 22, 7, 2, 1, 0, 0

Implications …

To the extent that trials with these features are more reliable and better suited to inform clinical care, research funders need to rethink whether the current preponderance of research funding awarded to small clinical trials is a good return on investment …. Perhaps move more quickly into large, definitive, randomized controlled trials evaluating clinical endpoints…

Devereaux PJ, Yusuf S. N Engl J Med 2013;369:962-
EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

GRUPPO ITALIANO PER LO STUDIO DELLA STREPTOCHINASI NELL’INFARTO MIOCARDICO (GISSI)*

Summary In an unblinded trial of intravenous streptokinase (SK) in early acute myocardial infarction, 11 806 patients in one hundred and seventy-six coronary care units were enrolled over 17 months. Patients admitted within 12 h after the onset of symptoms and with no contraindications to SK were randomised to receive SK in addition to usual treatment and complete data were obtained in 11 712. At 21 days overall hospital mortality was 10·7% in SK recipients versus 13% in controls, an 18% reduction (p = 0.0002, relative risk 0.81). The extent of the beneficial effect appears to be a function of time from onset of pain to SK infusion (relative risks 0·74, 0·80, 0·87, and 1·19 for the 0–3, 3–6, 6–9, and 9–12 h subgroups). SK seems to be a safe drug for routine administration in acute myocardial infarction.

“It started with no funding and skepticism in some quarters but today GISSI is recognized as an Italian achievement that has changed cardiology treatment worldwide.”

http://eurheartj.oxfordjournals.org/content/31/9/1023.full
“Current” Clinical Trial Business Model

Size
- Mostly small N
- Huge budgets

Endpoints
- Mostly surrogate

Setting
- Research enterprise – “parallel universe”
- Failure to leverage existing resources
- “High-grade” data – audited, monitored

Califf RM et al. JAMA 2012;307:1838-47
Disruptive Approach: Leverage …

The NEW ENGLAND JOURNAL of MEDICINE

Established in 1812
October 24, 2013
Vol. 369 No. 17

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform. Study design and rationale

Ole Frobert, MD, PhD, Bo Lagerqvist, MD, PhD, Thórarinn Guðnason, MD, PhD, FESC, Leif Thuesen, MD, PhD, Roger Svensson, MSci, Göran K. Olivecrona, MD, PhD, and Stefan K. James, MD, PhD. Örebro, Uppsala and Lund, Sweden; Reykjavik, Iceland; and Aarhus, Denmark

Frobert O et al. AHJ 2010;160:1042-8
Costs?

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

Cost (incremental) = US $300,000 ($50 per patient)
“As large trials became popular…the original simplicity was lost…leading to increasingly complex trials. The unintended consequence has been to threaten the very existence of RCTs, given the operational complexities and ensuring costs. An ideal opportunity would be to embed randomization in the EMR…introducing randomization into registries sponsored by societies.”
Disruptive Research in Action (Canada)

24,000 patients

< $ 2 million
Full Coverage for Preventive Medications after Myocardial Infarction


Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial

Christiansen EH et al. Lancet 2013;381:661-9
Network News: Powering Clinical Research

Joseph V. Selby,¹ Harlan M. Krumholz,²,³ Richard E. Kuntz,³,⁴ Francis S. Collins³,⁵,*

The Patient-Centered Outcomes Research Institute announces bold plans to build a National Patient-Centered Clinical Research Network that will unite millions of patients through a coordinated collaboration with researchers and health care delivery organizations.
At the NIH ...

Rethinking Clinical Trials: A Living Textbook of Pragmatic Clinical Trials

Collaboratory News

First patient enrolled in Collaboratory trial
01/13/14: The TiME Demonstration Project, led the University of Pennsylvania's Laura Dember, MD, has enrolled its first patient.

https://www.nihcollaboratory.org/Pages/default.aspx
**Department of Health and Human Services**

### Part 1. Overview Information

<table>
<thead>
<tr>
<th>Participating Organization(s)</th>
<th>National Institutes of Health (NIH)</th>
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| Components of Participating Organizations | National Heart, Lung, and Blood Institute (NHLBI)  
National Institute on Aging (NIA)  
National Institute on Deafness and Other Communication Disorders (NIDCD)  
National Institute on Drug Abuse (NIDA)  
National Institute of Nursing Research (NINR)  
National Center for Complementary and Alternative Medicine (NCCAM) |
| Funding Opportunity Title | Low-Cost, Pragmatic, Patient-Centered Randomized Controlled Intervention Trials (UH2/UH3) |
| Activity Code | UH2/UH3 Phase Innovation Awards Cooperative Agreement |
| Announcement Type | New |
| Related Notices | None |
| Funding Opportunity Announcement (FOA) Number | RFA-HL-14-019 |
| Companion Funding Opportunity | RFA-HL-14-020, R01 Research Project |

Many thanks to Denise Bonds and Nakela Cook
Concerns – What’s the Role of Research?

A HASTINGS CENTER REPORT
SPECIAL REPORT

ETHICAL OVERSIGHT

In Support of SUPPORT — A View from the NIH
Kathy L. Hudson, Ph.D., Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D.

The “LEVI’S” Approach to Innovative Trials

- **L**
  - Large
  - LEveraged

- **E**
  - Embedded
  - Ethical
  - Equipoise

- **V**aluable

- **I’**
  - Inexpensive
  - Innovative

- **S**
  - Sound Science