Perspectives on Large Simple Trials

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Clinical Trials Transformation Initiative

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Matthew Fontaine Maury

- “Depot of Charts and Instruments”
- “Patterns Everywhere”
- Inventories of barometers, compasses, sextants, chronometers, log-books, maps, and charts – “rubbish”
- Standard log forms and “bottles in the sea”

Mayer-Schonberger V, Cukier K, Houghton Miflin, 2013
The Result: Data as A Disruptive Technology

- 1.2 million data points
- Transformed shipping
- “Conceived outside traditional academic circles”
- “Unearthing data from material that no one thought had any value”
- Data use many times

http://www.raremaps.com/gallery/detail/18671?view=print
“But it was filmless photography, so management’s reaction was, ‘That’s cute, but don’t tell anyone about it.’”

Steve Sasson, quoted in the *NY Times*, May 20, 2008
A Recurring Pattern: All Dismissed
One Difference: Our Models are Failing

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.

Rosbash M. Science 2011; 333:136
“Classic” Clinical Trial Business Model

Size
- Mostly small N
- Huge budgets

Endpoints
- Mostly surrogate
- Clinical trials employ adjudication

Setting
- Research enterprise – “parallel universe”
- “High-grade” data – audited, monitored

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

Califf RM et al. JAMA 2012;307:1838-47
Looking Back at a Disruptive Technology

EFFECTIVENESS OF INTRAVENTOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

GRUPPO ITALIANO PER LO STUDIO DELLA STREPTOCHINASIS 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.

“The Lancet · Saturday 22 February 1986

“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
We’ve Done This Before!

Protocol:

Trial to Evaluate the Effect of Digitalis on Mortality in Heart

Failure:

Digitalis Investigation Group (DIG)

Baseline Form

Randomization Number

Local Center Name

PRINT Patient Name

Date of Randomization

Items 1 through 9 must be transmitted over the telephone at the time of randomization.

1. Social Security Number
2. Date of Birth
3. Ejection Fraction (percent)
   A. Method (1=Radiouclide, 2=Angiography, 3=2-D Echo)
4. Sex (1=Male, 2=Female)

Thanks to Nancy Geller
Robust Findings


N = 6800
HR = 0.99, 95% 0.91 – 1.07
Practical Clinical Trials
Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy

Sean R. Tunis, MD, MSc
Daniel B. Stryer, MD
Carolyn M. Clancy, MD

Decision makers in health care are increasingly interested in high-quality scientific evidence to support clinical and health policy decisions, but the quality of available scientific evidence is often limited.

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 Fröbert, MD, PhD, Bo Lagerqvist, MD, PhD, Thórarinn Gudnason, 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
Disruptive Research in Action (Scandinavia)

Cost (incremental) = US $300,000 ($50 per patient)
Disruptive Research in Action (Canada)

24,000 patients

< $ 2 million
“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.”
Patient-Initiated Internet Research

Accelerated clinical discovery using self-reported patient data collected online and a patient-matching algorithm

Paul Wicks, Timothy F Vaughan, Michael P Massagli & James Heywood

“Attempting to establish the efficacy of a treatment in a prospective manner inevitably draws comparisons with methodologies that have the highest standards of rigor, and by comparison this discipline is in its infancy.”
“New” Disruptive Large, Simple Trials

Size – both bigger and smaller
- Huge N – robust estimates, heterogeneity
- Streamlined budgets – grows a bigger pie

Endpoints – what really matters
- Patient-oriented with minimal adjudication

Setting – increasingly integrated world
- Within patient-care units and communities
- Leverage digital data sources
- Patients as partners, not subjects
How Do We Get There?

Embed into existing projects
Create “small sub-organizations”
  - Generate excitement
  - Thrilled with “small wins”
Fail early, often, and inexpensively
Look for new markets
Restructure incentives
Think “LEVI’S”

New Business Models for Large Simple Trials

- L
  - Large
  - LEveraged

- E
  - Embedded
  - External

- V
  - Valuable

- I’
  - Inexpensive
  - Innovative

- S
  - Sound Science