Perspectives on Large Simple Trials

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Clinical Trials Transformation Initiative

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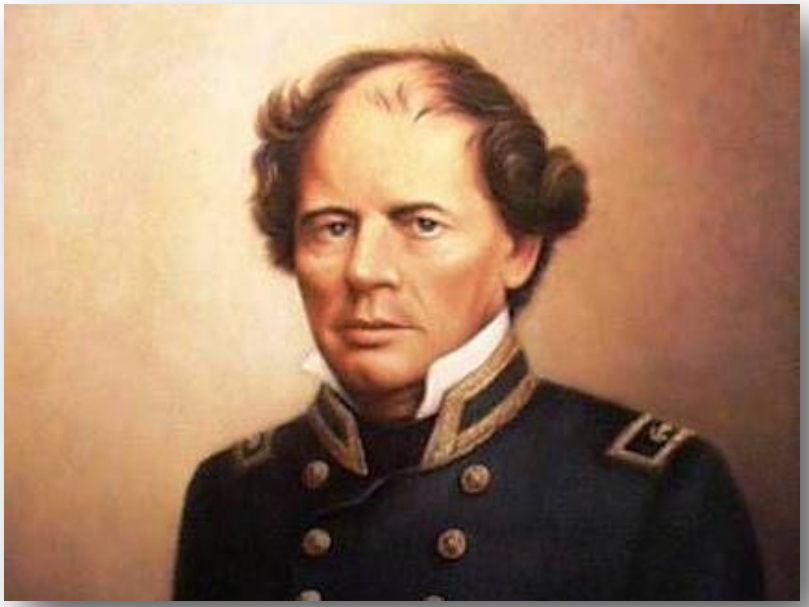
National Heart, Lung, and Blood Institute

Matthew Fontaine Maury

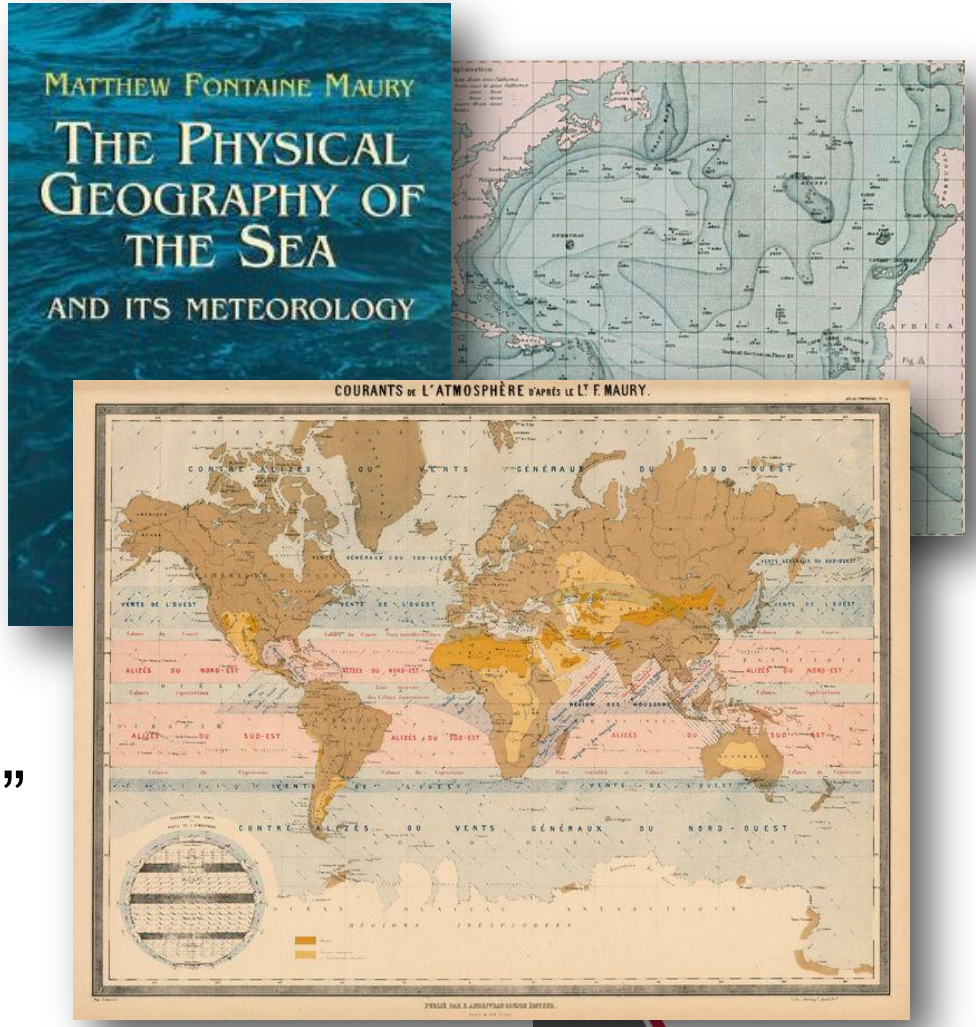
- “Depot of Charts and Instruments”
- “Patterns Everywhere”
- Inventories of barometers, compasses, sextants, chronometers, log-books, maps, and charts – “rubbish”
- Standard log forms and “bottles in the sea”



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



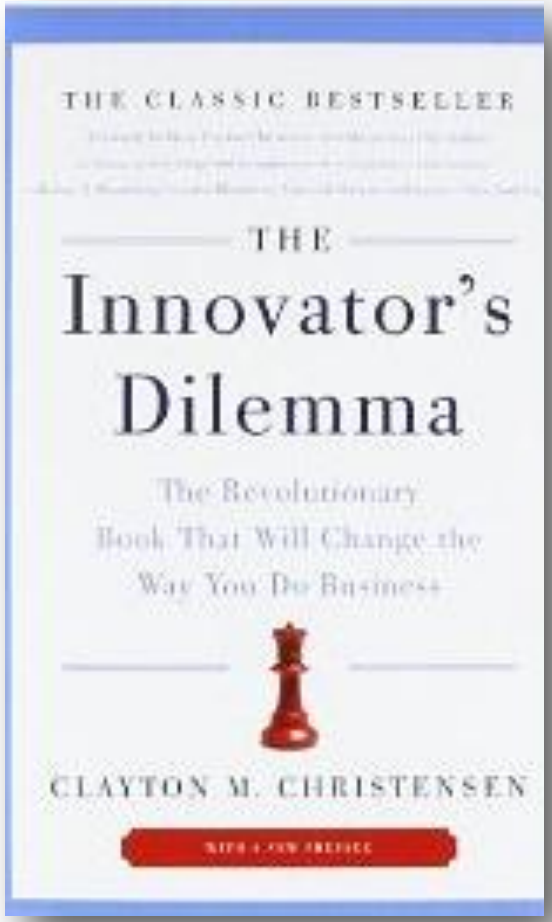
http://www.raremaps.com/gallery/detail/18671?view=print

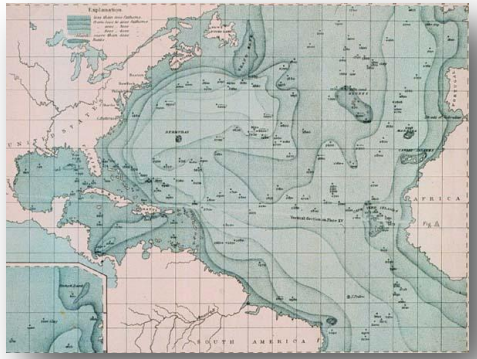
A More Recent Disruptive Technology

"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





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One Difference: Our Models are Failing

EDITORIAL

A Threat to Medical Innovation

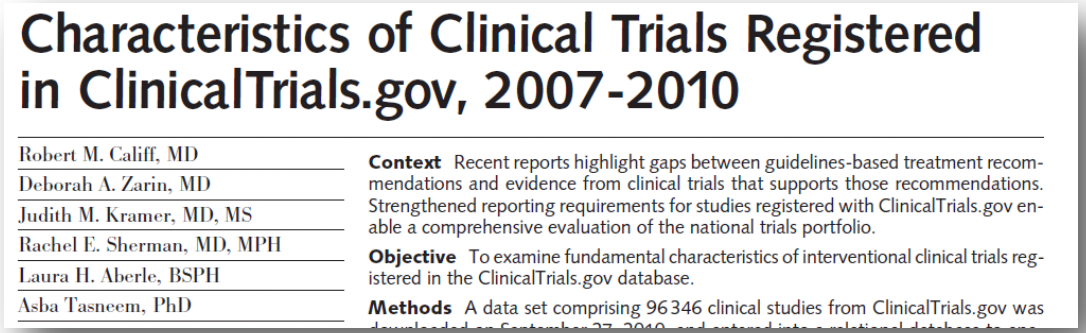
With 10 to 15% paylines at some institutes (or even less), the current situation makes grant evaluation nearly impossible and is putting truly excellent laboratories out of business. In the spirit of "never waste a good crisis," a serious evaluation of many NIH extramural policies and programs is warranted. 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



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

Robert M. Califf, MD
Deborah A. Zarin, MD
Judith M. Kramer, MD, MS
Rachel E. Sherman, MD, MPH
Laura H. Aberle, BSPH
Asba Tasneem, PhD

Context Recent reports highlight gaps between guidelines-based treatment recommendations and evidence from clinical trials that supports those recommendations. Strengthened reporting requirements for studies registered with ClinicalTrials.gov enable a comprehensive evaluation of the national trials portfolio.

Objective To examine fundamental characteristics of interventional clinical trials registered in the ClinicalTrials.gov database.

Methods A data set comprising 96 346 clinical studies from ClinicalTrials.gov was

Endpoints

- Mostly surrogate
- Clinical trials employ adjudication

Setting

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

Califf RM et al. JAMA 2012;307:1838-47

Looking Back at a Disruptive Technology

EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

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

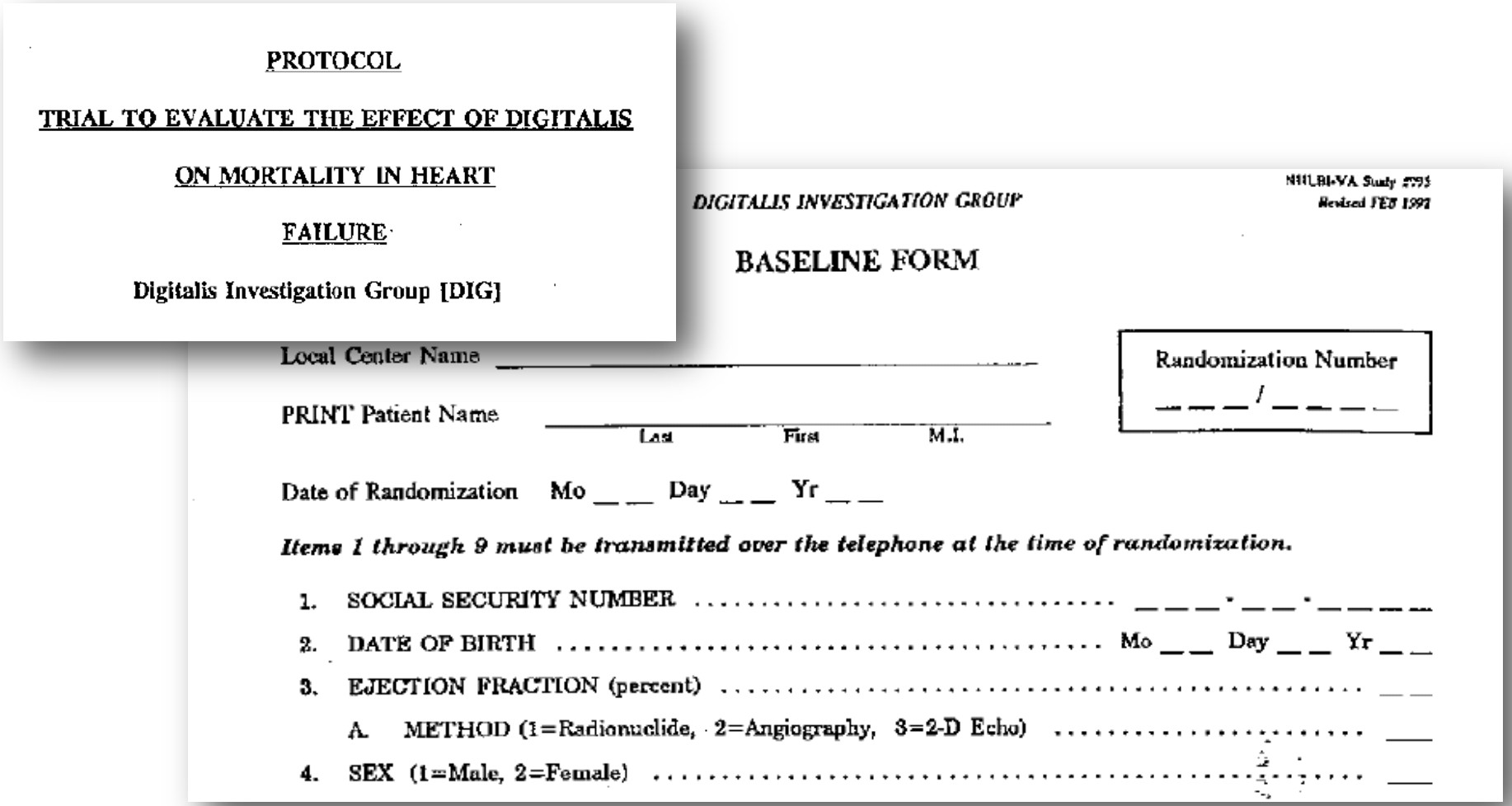
Summary In an unblinded trial of intravenous streptokinase (SK) in early acute myocardial infarction, 11 806 patients in one hundred and seventy-six coronary care units were enrolled over 17 months. Patients admitted within 12 h after the onset of symptoms and with no contraindications to SK were randomised 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.

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]

DIGITALIS INVESTIGATION GROUP

NHLBI-VA Study #795
Revised FEB 1991

BASELINE FORM

Local Center Name _____

Randomization Number
___ ___ / ___ ___ ___ ___

PRINT Patient Name _____
Last First M.I.

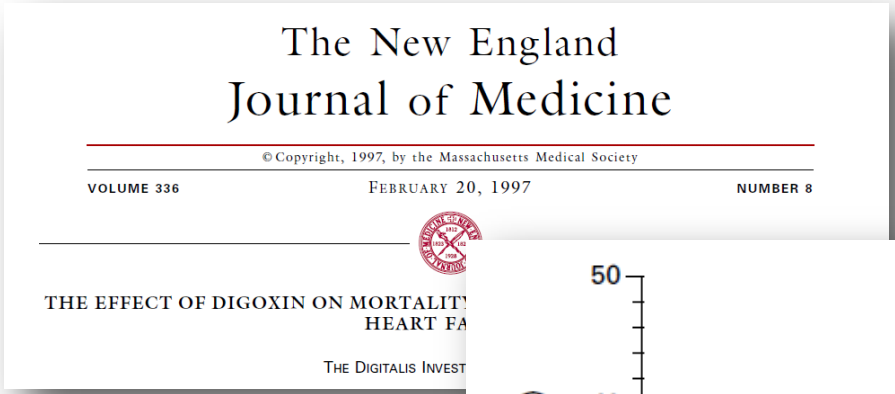
Date of Randomization Mo ___ Day ___ Yr ___

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

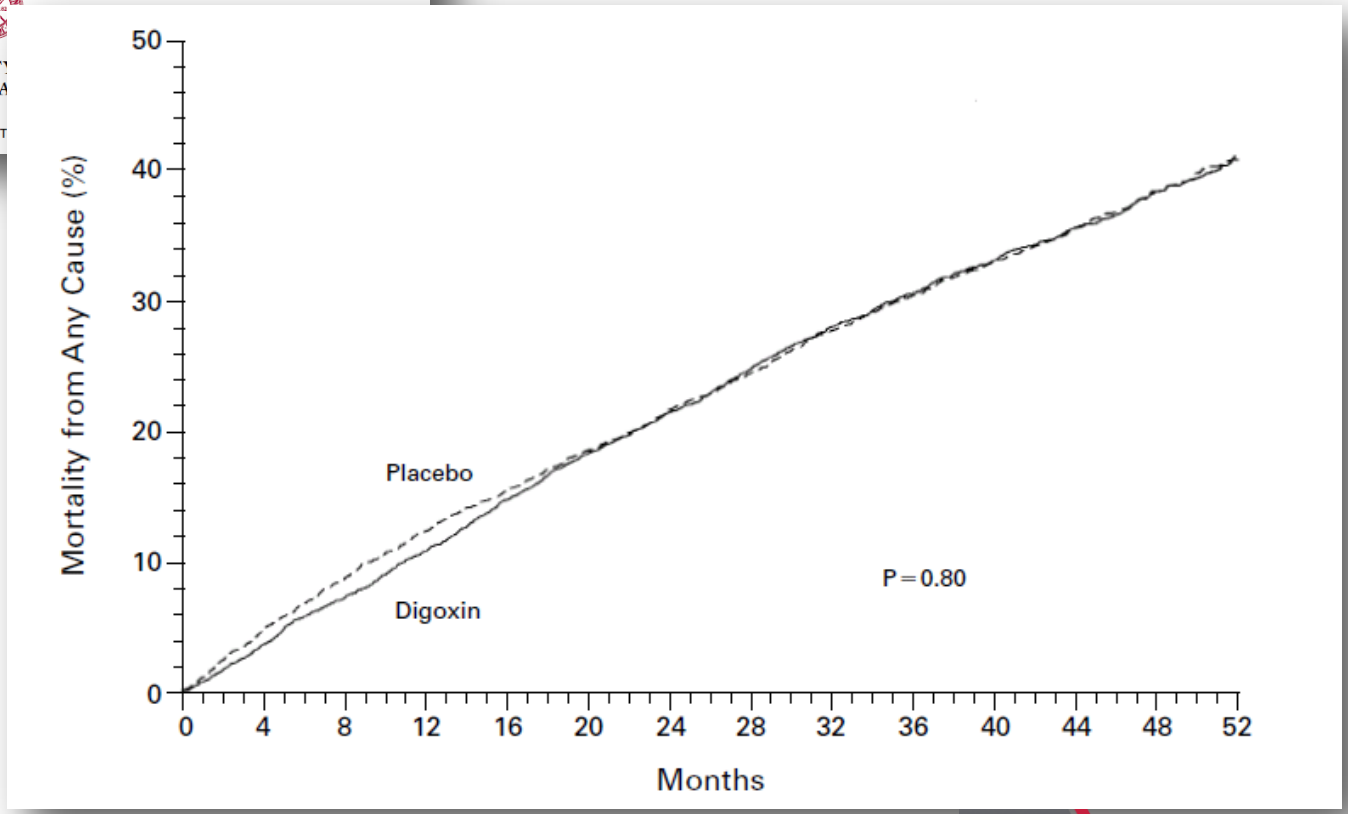
1. SOCIAL SECURITY NUMBER ..... ___ ___ ___ - ___ ___ - ___ ___ ___ ___
2. DATE OF BIRTH ..... Mo ___ Day ___ Yr ___
3. EJECTION FRACTION (percent) ..... ___
   A. METHOD (1=Radionuclide, 2=Angiography, 3=2-D Echo) ..... ___
4. SEX (1=Male, 2=Female) ..... ___

Thanks to Nancy Geller

Robust Findings



N = 6800
HR = 0.99, 95% 0.91 – 1. 07



DIG Group. N Engl J Med 1997;336:525-33

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Disruptive Thoughts in the Here and Now

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 interest
quality scientific evidence to support clinical and health po
ever, the quality of available scientific evidence is often

JAMA®

AHJ American Heart Journal

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,[a] Bo Lagerqvist, MD, PhD,[b] Thórarinn Gudnason, MD, PhD, FESC,[c] Leif Thuesen, MD, PhD,[d] Roger Svensson, MSci,[c] Göran K. Olivecrona, MD, PhD,[f] and Stefan K. James, MD, PhD[b] *Örebro, Uppsala and Lund, Sweden; Reykjavik, Iceland; and Aarhus, Denmark*

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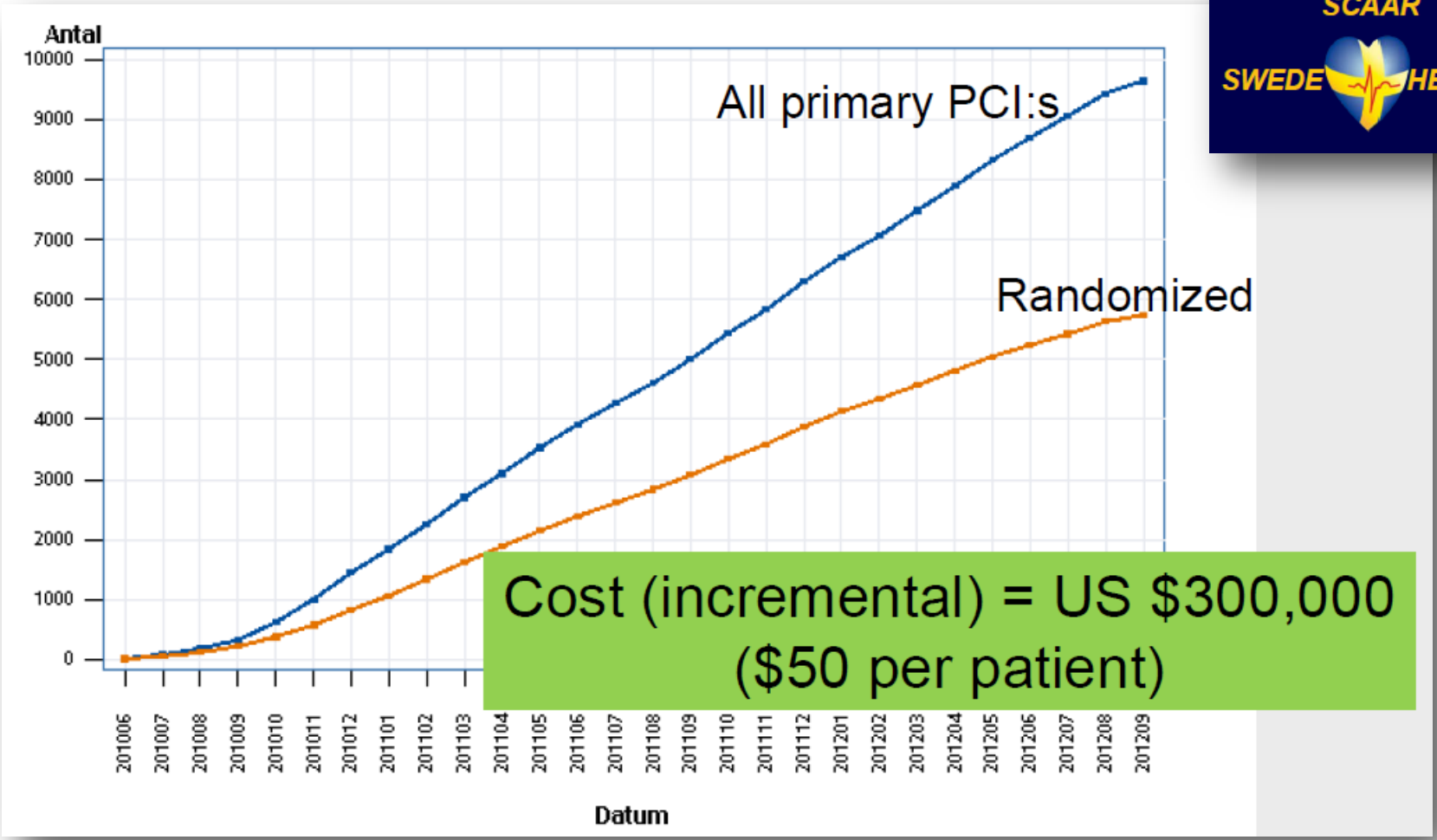
Tunis SR et al. JAMA 2003;290:1624-32
Frobert O et al. AHJ 2010;160:1042-8

Disruptive Research in Action (Scandinavia)



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Disruptive Research in Action (Canada)

24,000 patients

< $ 2 million

Others are Singing the Same Tune

VIEWPOINT

Transforming Clinical Trials in Cardiovascular Disease

Mission Critical for Health and Economic Well-being

Elliott M. Antman, MD
Robert A. Harrington, MD

Perhaps the most exciting opportunity for CVD research-ers is to capitalize on the advances in systems and computa-tional biology that can inform first-in-human, proof-of-

"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."

Antman E, Harrington RA. JAMA 2012;338:1743-4.

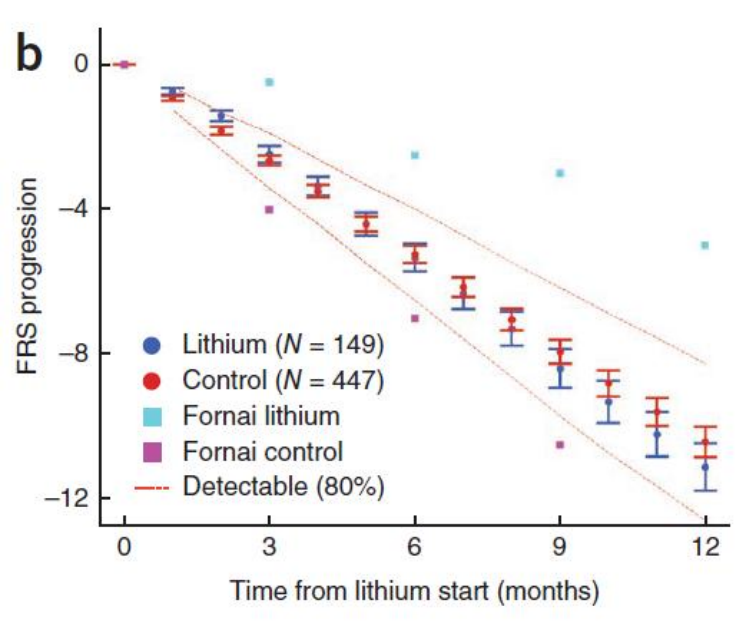
Patient-Initiated Internet Research

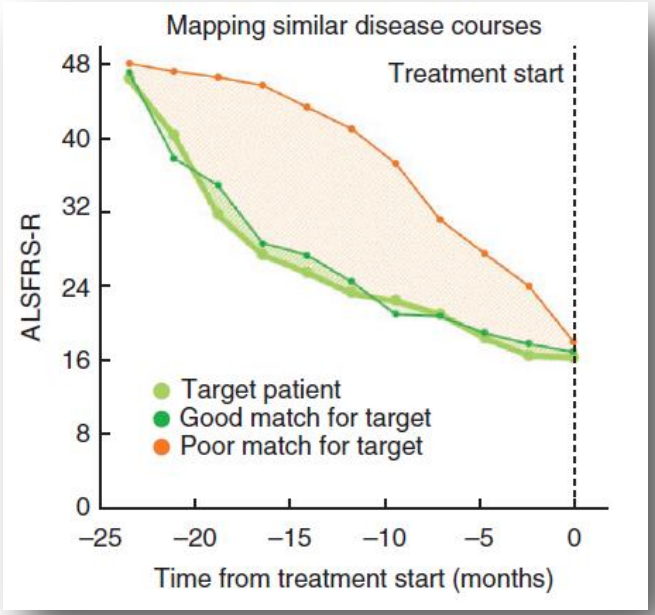
_computational BIOLOGY

ANALYSIS

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

Paul Wicks, Timothy E 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."

Wicks P et al. Nature Biotechnology 2011;29:411-414

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“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”

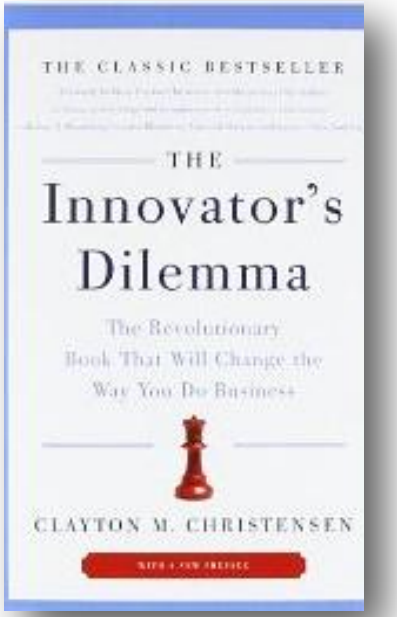
- Generate excitement
- Thrilled with “small wins”

Fail early, often, and inexpensively

Look for new markets

Restructure incentives

Think “LEVI’S”



NIH Collaboratory

Health Care Systems Research Collaboratory

Rethinking Clinical Trials

Christensen C. Harper Business 2000.

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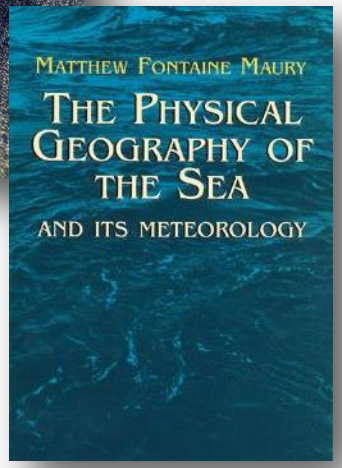
New Business Models for Large Simple Trials

- **L**
  - Large
  - LEveraged
- **E**
  - Embedded
  - External
- **V**aluable
- **I’**
  - Inexpensive
  - Innovative
- **S**
  - Sound Science



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