

Pragmatic Trials and Novel Interventional Cohort Studies

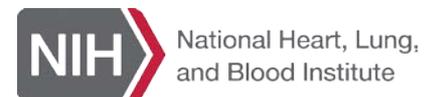
Michael S Lauer, MD, FACC, FAHA

Director, Division of Cardiovascular Sciences
National Heart, Lung, and Blood Institute

Financial disclosures: None

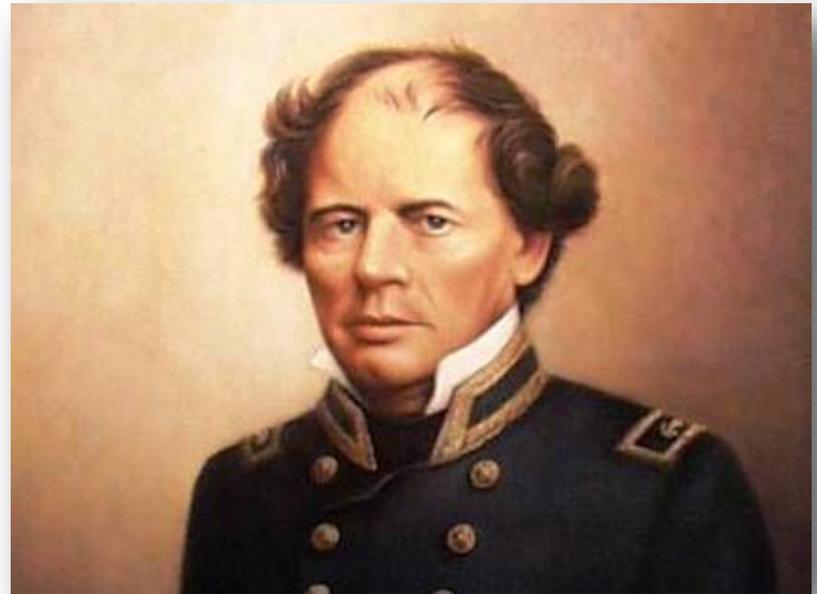
BD2K Workshop: Enabling Research Use of Clinical Data

September 11, 2013



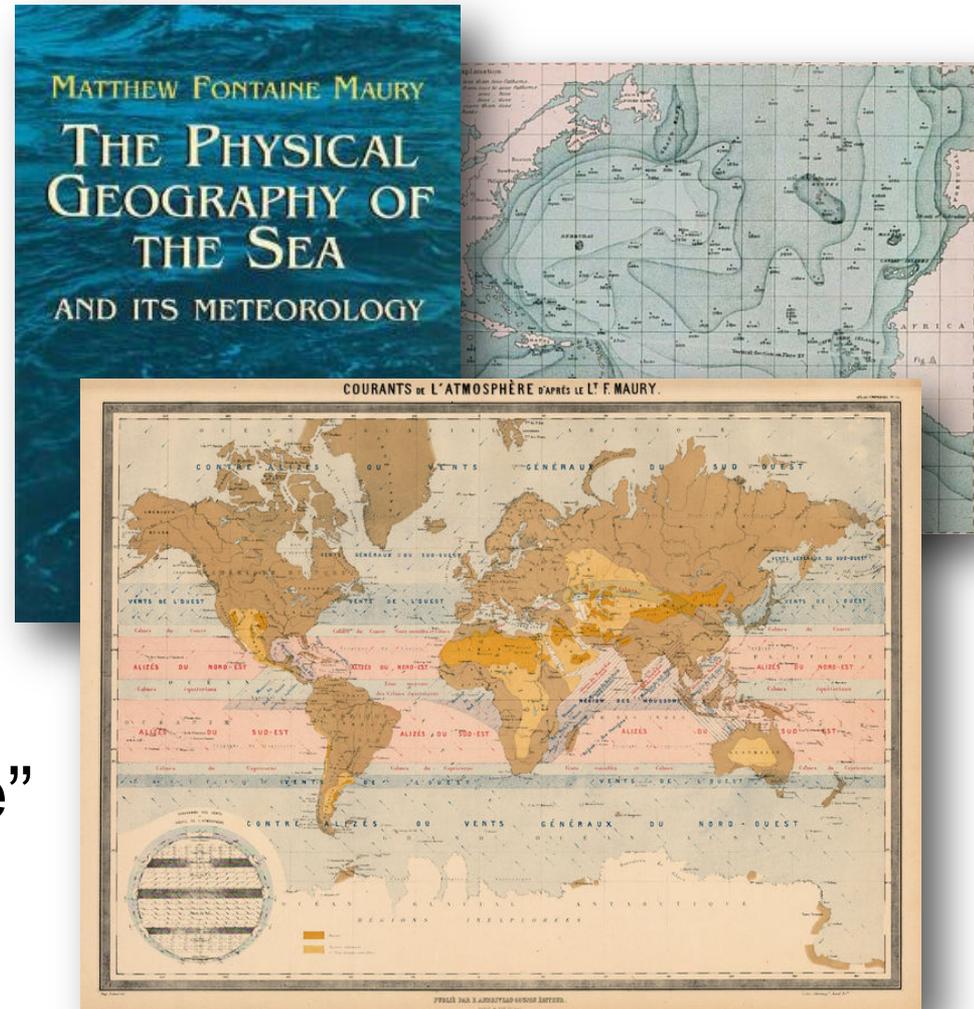
Matthew Fontaine Maury

- “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”



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



“Datafication”

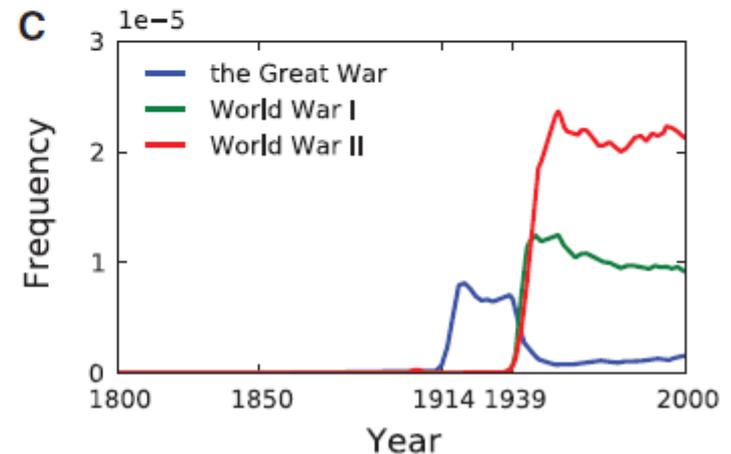
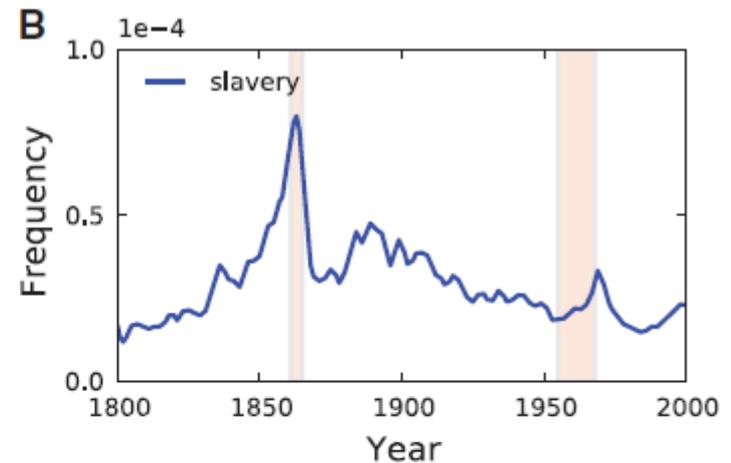
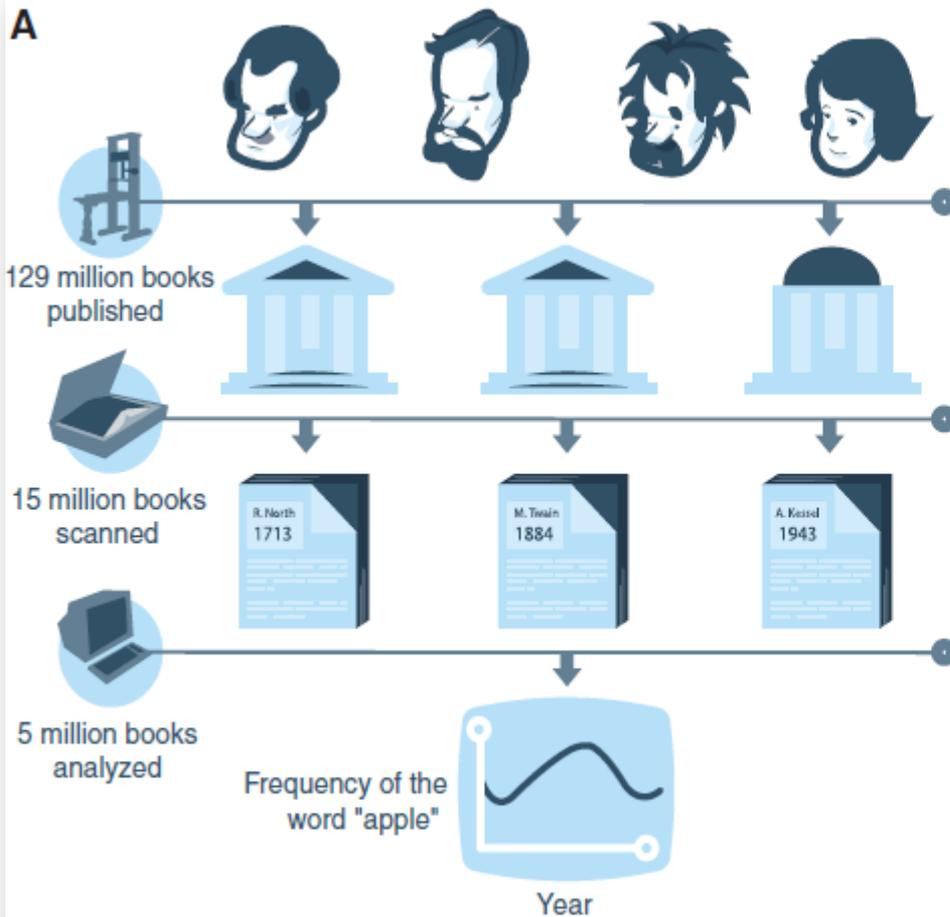
- Render virtually anything into data
- “Like other infrastructural advances it will bring fundamental changes ... different mindset”
- OK to re-use data
- $N = \text{All}$



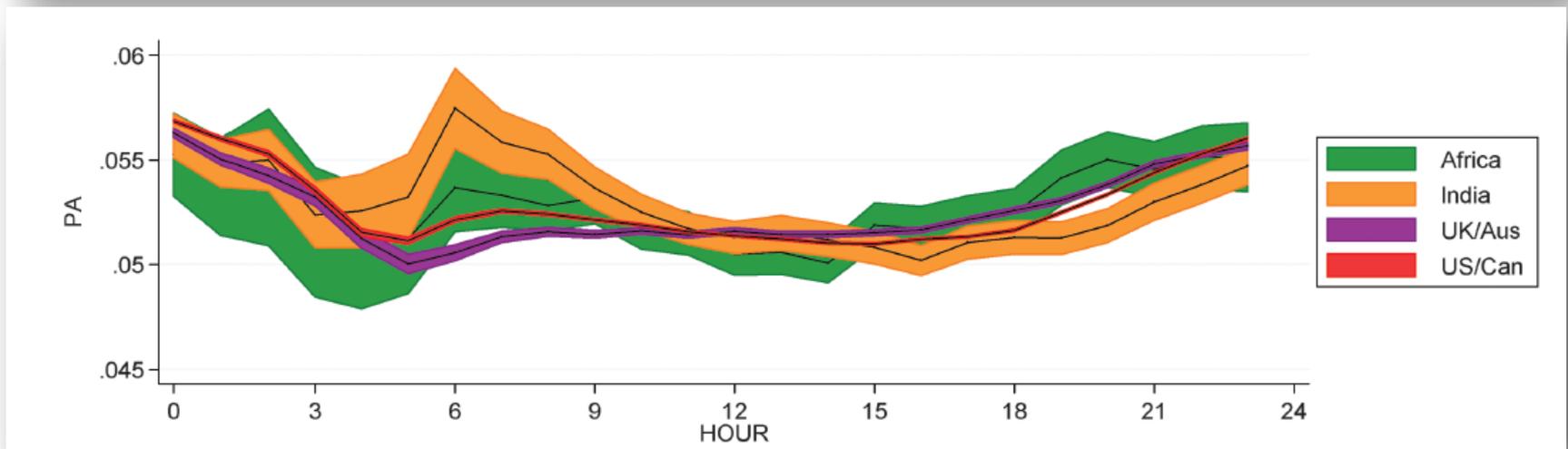
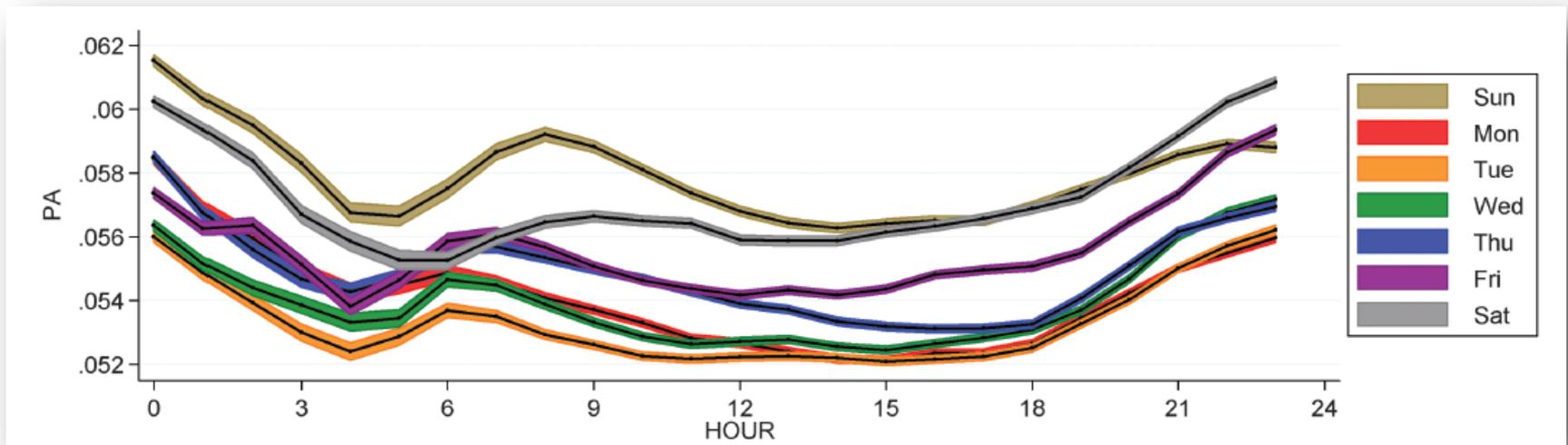
Datafication is Here

Quantitative Analysis of Culture Using Millions of Digitized Books

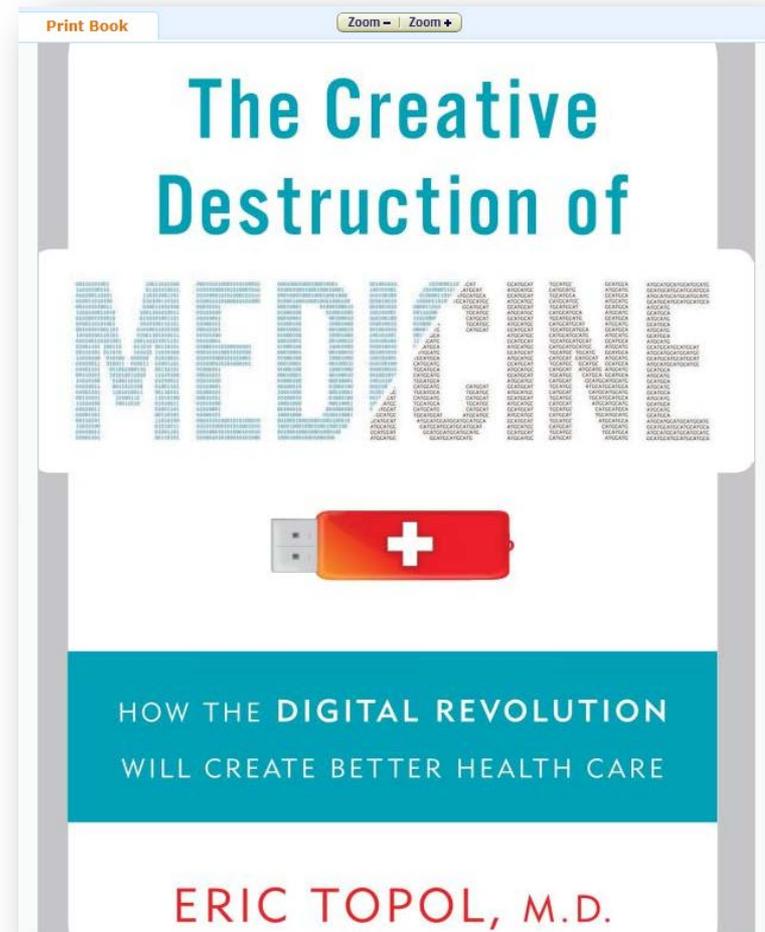
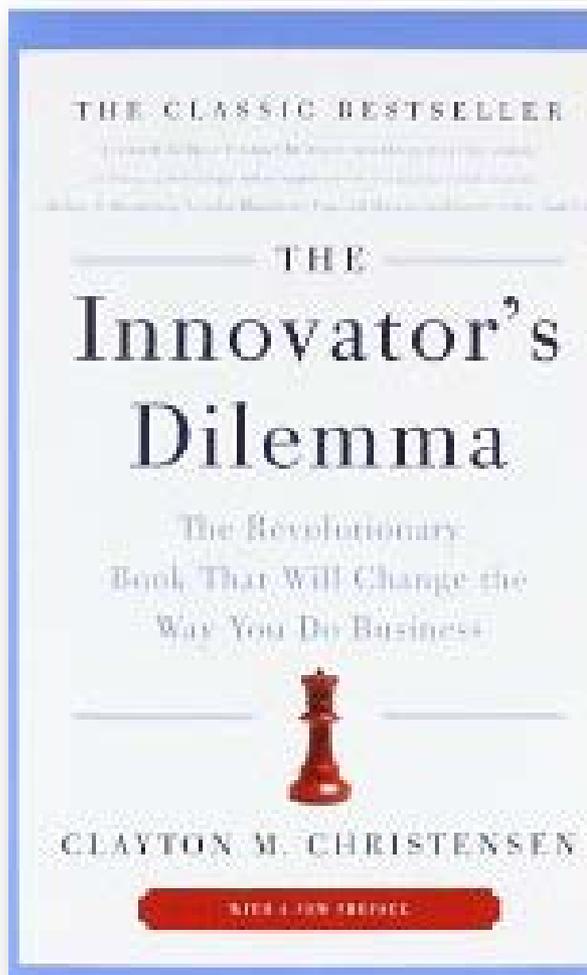
Jean-Baptiste Michel,^{1,2,3,4,5,*†} Yuan Kui Shen,^{2,6,7} Aviva Presser Aiden,^{2,6,8} Adrian Veres,^{2,6,9}
Matthew K. Gray,¹⁰ The Google Books Team,¹⁰ Joseph P. Pickett,¹¹ Dale Hoiberg,¹²
Dan Clancy,¹⁰ Peter Norvig,¹⁰ Jon Orwant,¹⁰ Steven Pinker,⁵



Useful Data from Twitter?!



Disruptive, Creative Destruction



Why We Must Pay Attention



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.***

“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

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 downloaded on September 27, 2010, and entered into a relational database. An

One Kind of Disruption: Integration into Care

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 ($p=0\cdot0002$, 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.”

Disruption: Keep it VERY Simple

PROTOCOL

TRIAL TO EVALUATE THE EFFECT OF DIGITALIS

ON MORTALITY IN HEART

FAILURE

Digitalis Investigation Group [DIG]

DIGITALIS INVESTIGATION GROUP

NIH/HLI-VA Study #795
Revised FEB 1997

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) ____

Robust Findings

The New England Journal of Medicine

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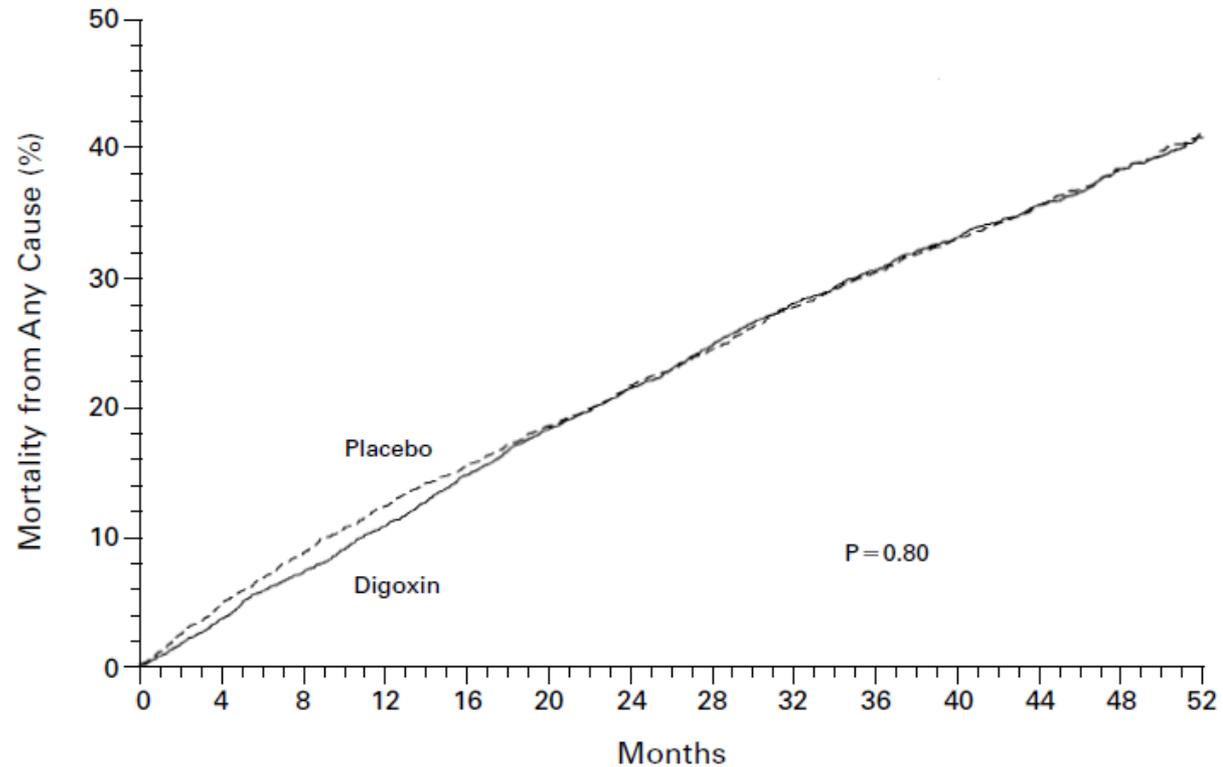
THE EFFECT OF DIGOXIN ON MORTALITY
IN PATIENTS WITH HEART FAILURE

THE DIGITALIS INVESTIGATION



N = 6800

HR = 0.99, 95% 0.91 – 1.07



Disruptive Thoughts: Pragmatic, Integrated

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. However, the quality of available scientific evidence is often

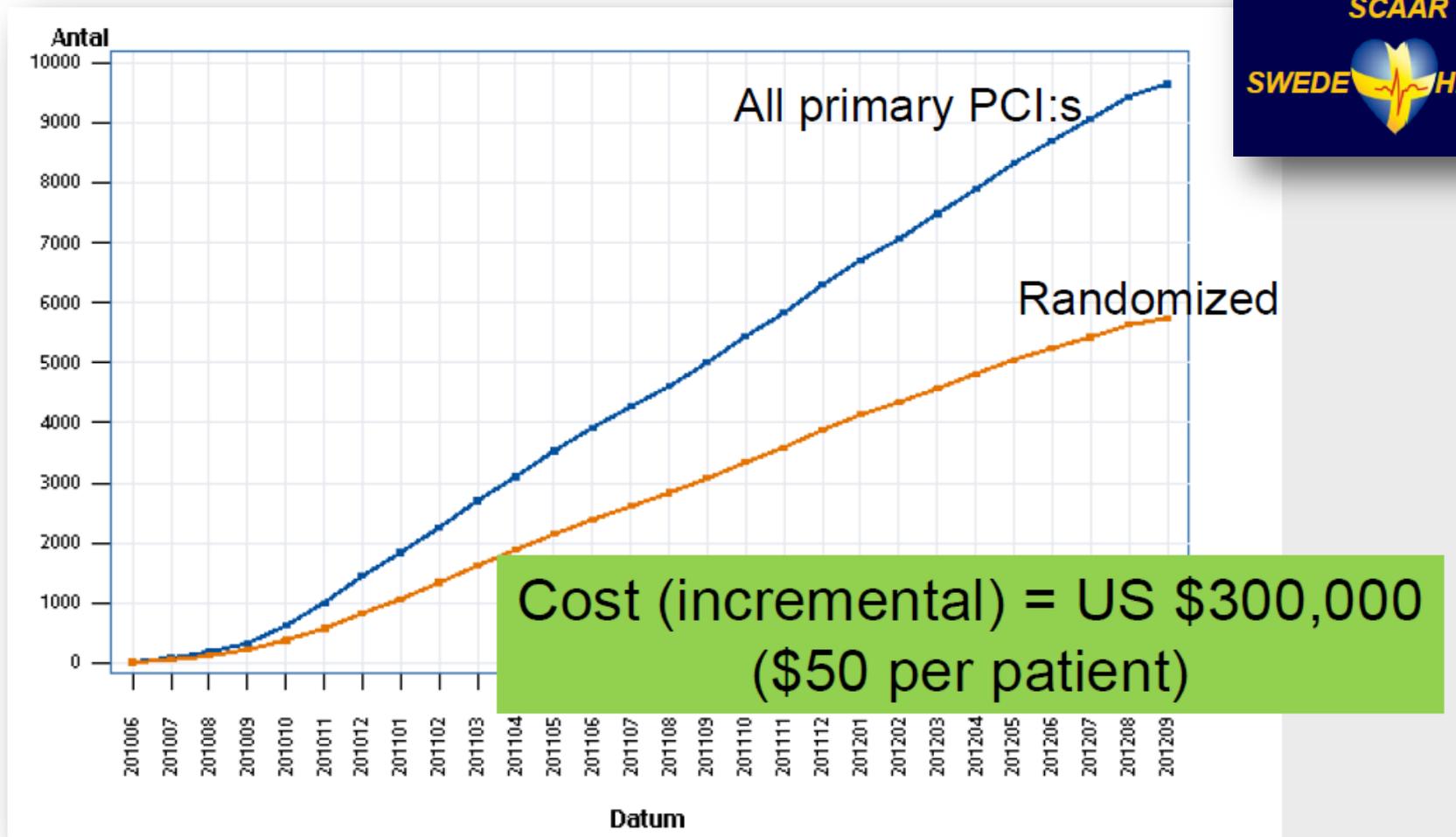
JAMA[®]



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, MSc,^e Göran K. Olivecrona, MD, PhD,^f and Stefan K. James, MD, PhD^b Örebro, Uppsala and Lund, Sweden; Reykjavik, Iceland; and Aarhus, Denmark

Disruptive Research in Action (Scandinavia)

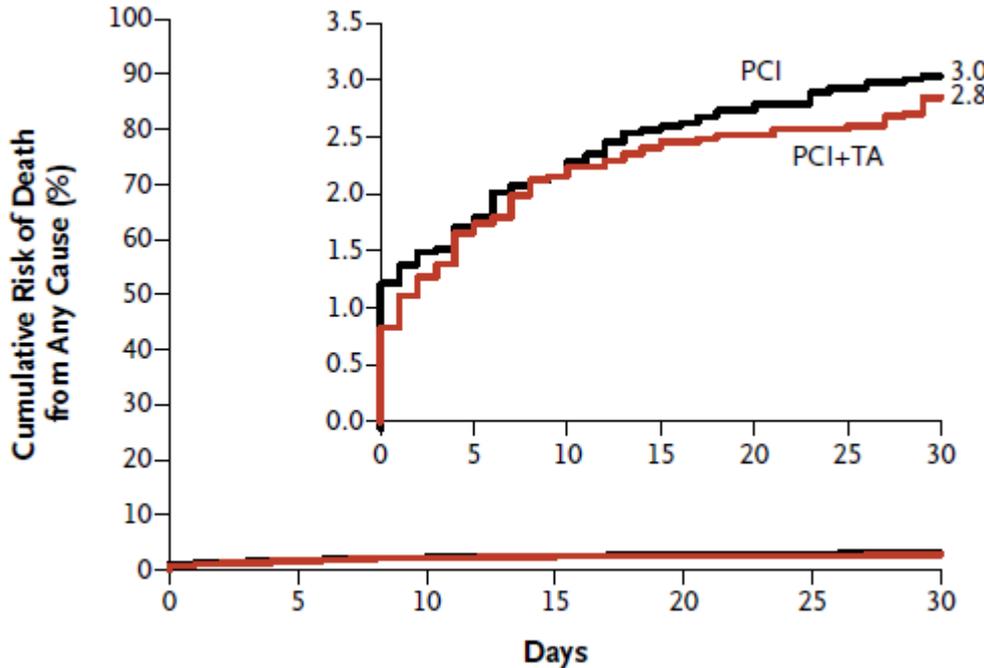


It Can Be Done ..

ORIGINAL ARTICLE

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

D., Bo Lagerqvist, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D.,
vic, M.D., Ph.D., Thorarinn Gudnason, M.D., Ph.D.,
D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerås, M.D.,
D., Mikael Danielewicz, M.D., David Erlinge, M.D., Ph.D.,
D., Ulf Jensen, M.D., Ph.D., Agneta C. Johansson, M.D.,
M.D., Johan Nilsson, M.D., Ph.D., Lotta Robertson, M.D.,
hall, M.D., Iwar Sjögren, M.D., Ollie Östlund, Ph.D.,
sk, M.D., Ph.D., and Stefan K. James, M.D., Ph.D.



The NEW ENGLAND JOURNAL of MEDICINE

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

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

Other 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 researchers is to capitalize on the advances in systems and computational 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.”

Use the EMR

The NEW ENGLAND JOURNAL of MEDICINE

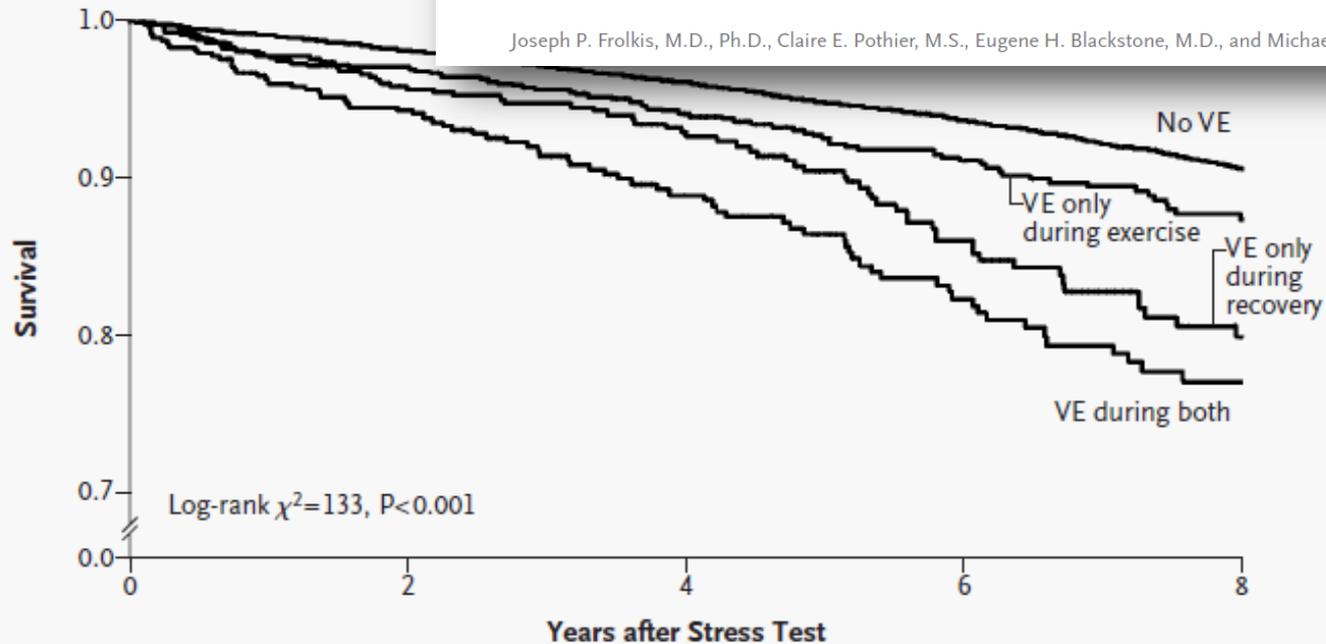
ESTABLISHED IN 1812

FEBRUARY 27, 2003

VOL. 348 NO. 9

Frequent Ventricular Ectopy after Exercise as a Predictor of Death

Joseph P. Frolkis, M.D., Ph.D., Claire E. Pothier, M.S., Eugene H. Blackstone, M.D., and Michael S. Lauer, M.D.



No. at Risk

No VE	27,219	26,295	22,900	19,576	16,708	13,971	11,283	9292	6480
VE only during exercise	945	900	840	687	598	504	418	352	255
VE only during recovery	589	564	474	425	331	276	226	162	121
VE during both	491	459	403	329	265	231	190	148	122

Disruptive EMR Research in Action (Canada)



Latest News About TORC Research Program Seminars & Events Pres

Transfusion Outcomes Research Collaborative

BREAKING NEWS:

We are also very pleased to announce that the TORC endorsed INFORM study has been successfully funded by the Canadian Institutes for Health Research for C\$1,606,292 over four years.



24,000 patients

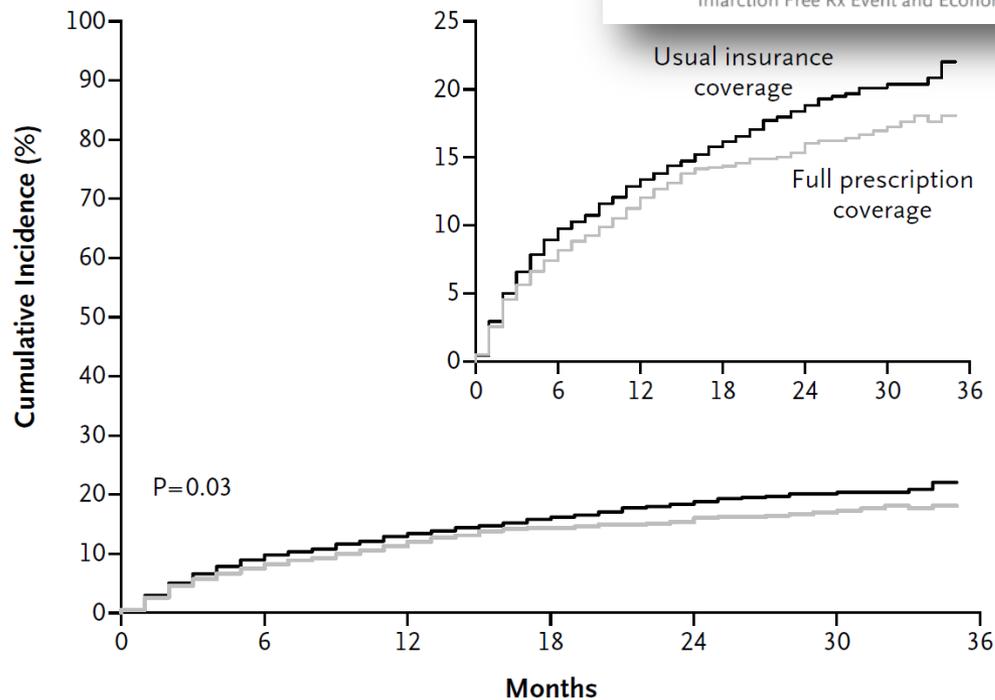
< \$ 2 million

Insurance Company!

Full Coverage for Preventive Medications after Myocardial Infarction

Niteesh K. Choudhry, M.D., Ph.D., Jerry Avorn, M.D., Robert J. Glynn, Sc.D., Ph.D., Elliott M. Antman, M.D., Sebastian Schneeweiss, M.D., Sc.D., Michele Toscano, M.S., Lonny Reisman, M.D., Joaquim Fernandes, M.S., Claire Spettell, Ph.D., Joy L. Lee, M.S., Raisa Levin, M.S., Troyen Brennan, M.D., J.D., M.P.H., and William H. Shrank, M.D., M.S.H.S., for the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial

First Fatal or Nonfatal Vascular Event



No. at Risk

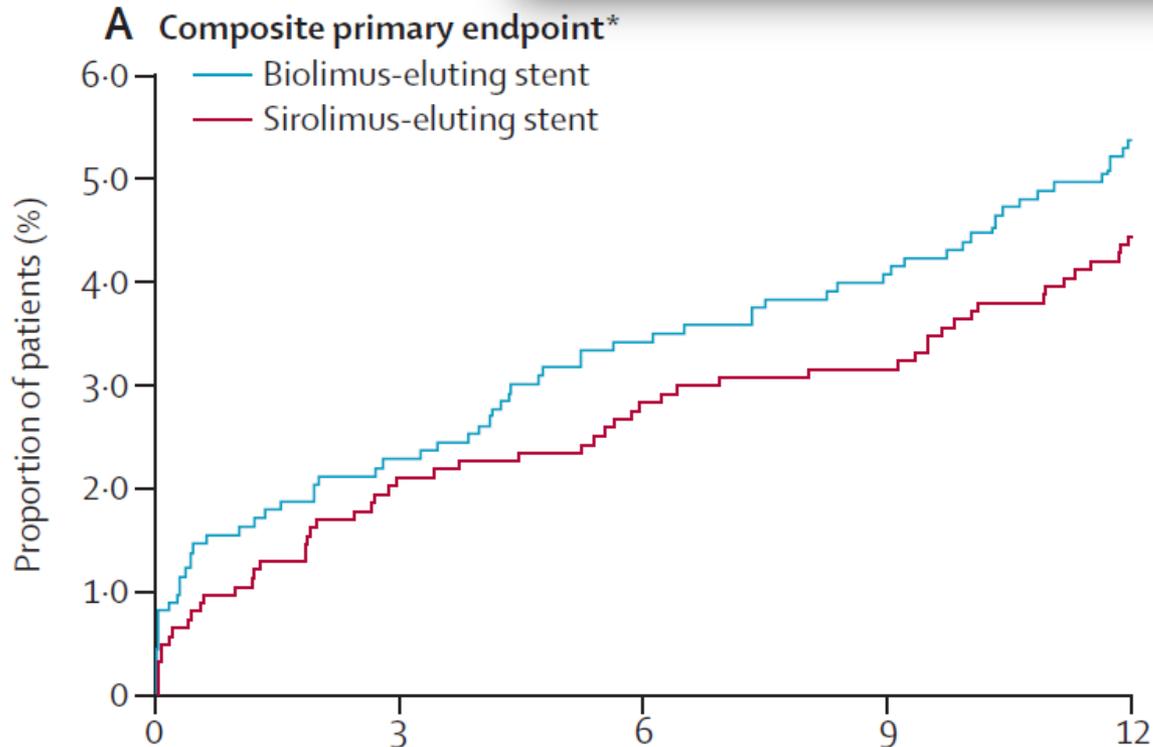
Usual insurance coverage	3010	2361	1652	1099	662	379	131
Full prescription coverage	2845	2295	1572	1013	625	340	135

National Cohort

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



Evdold Høj Christiansen, Lisette Okkels Jensen, Per Thyayssen, Hans-Henrik Tilsted, Lars Romer Krusell, Knud Nørregaard Hansen, Anne Kalkof, Michael Maeng, Steen Dalby Kristensen, Hans Erik Bøtker, Christian Juhl Terkelsen, Anton Boel Villadsen, Jan Ravkilde, Jens Aarøe, Morten Madsen, Leif Thuessen, Jens Flensted Lassen, for the Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT) V investigators



Number at risk

Biolimus-eluting stent	1229	1196	1176	1166	1146
Sirolimus-eluting stent	1239	1211	1199	1190	1171

Disruptive Design

The NEW ENGLAND
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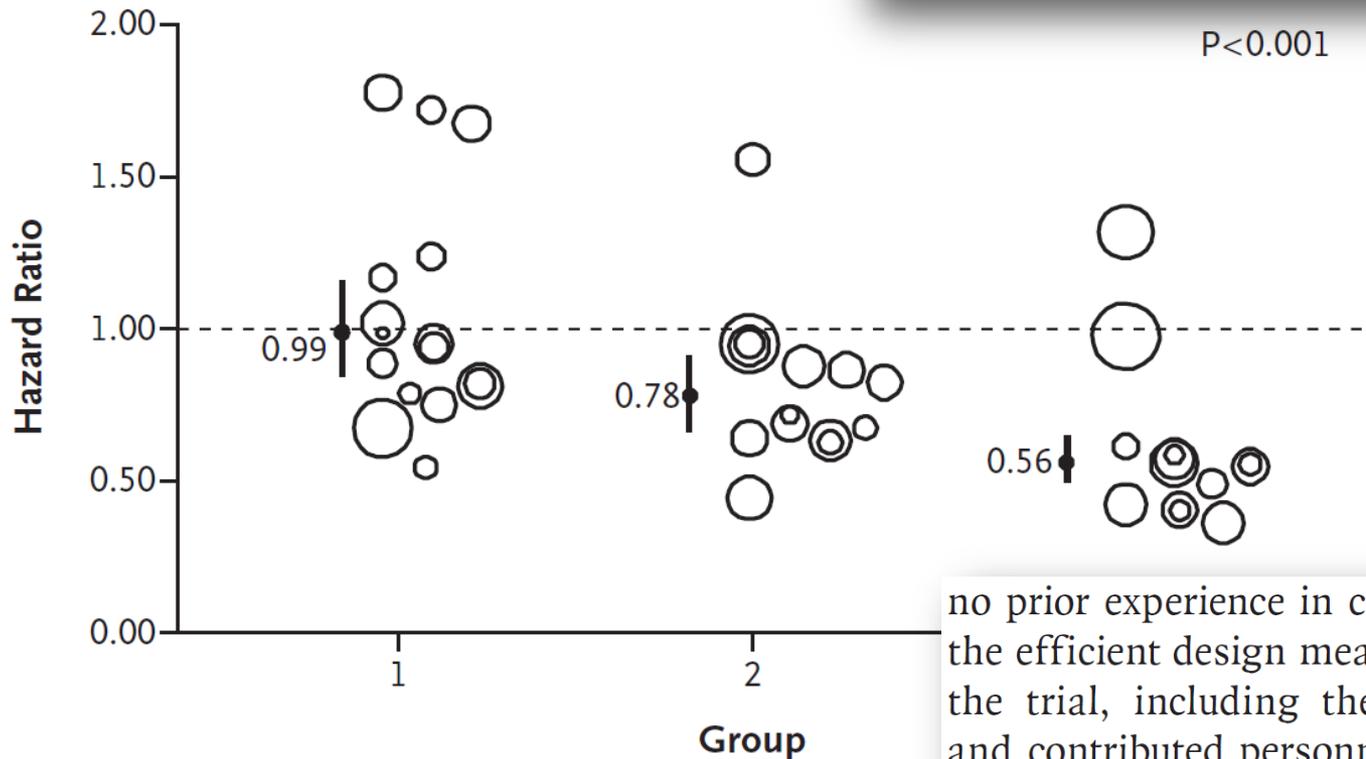
JUNE 13, 2013

VOL. 368 NO. 24

Targeted versus Universal Decolonization to Prevent ICU Infection

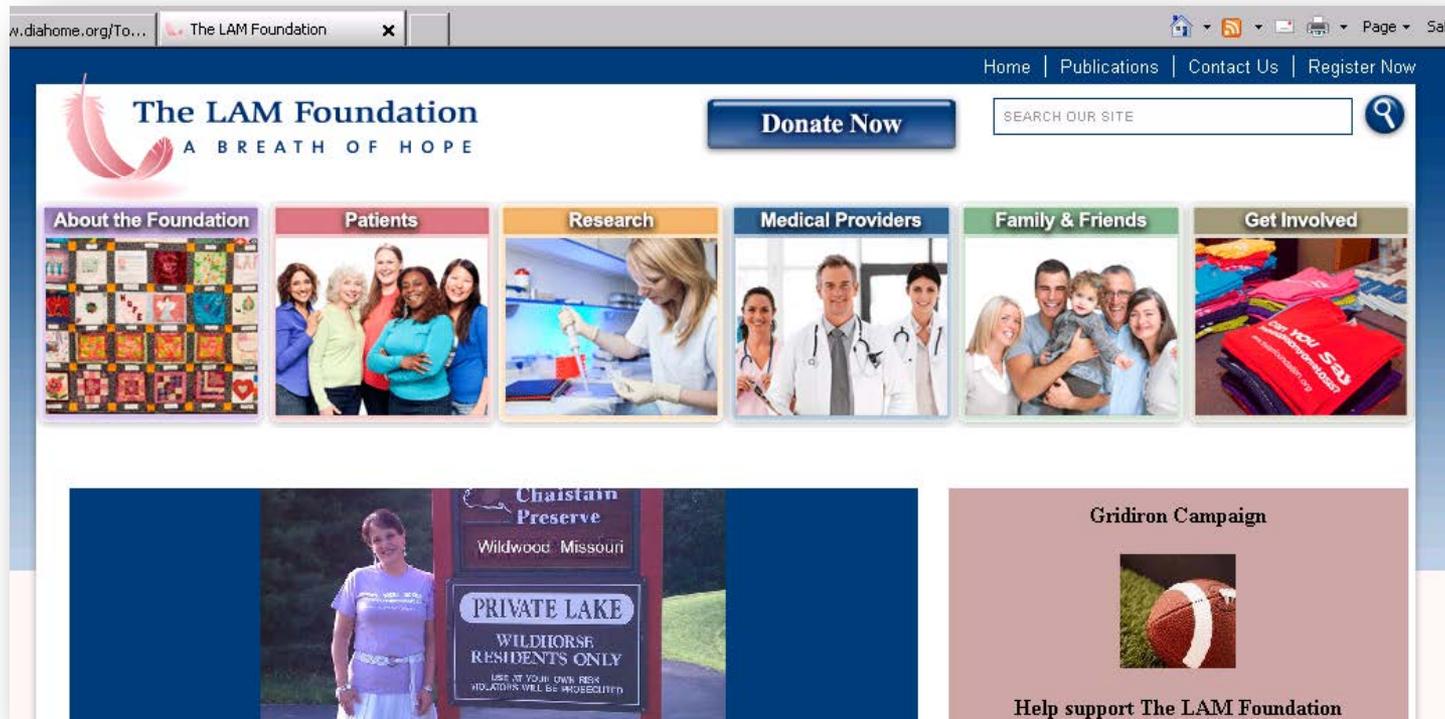
Susan S. Huang, M.D., M.P.H., Edward Septimus, M.D., Ken Kleinman, Sc.D., Julia Moody, M.S., Jason Hickok, M.B.A., R.N., Taliser R. Avery, M.S., Julie Lankiewicz, M.P.H., Adrijana Gombosev, B.S., Leah Terpstra, B.A., Fallon Hartford, M.S., Mary K. Hayden, M.D., John A. Jernigan, M.D., Robert A. Weinstein, M.D., Victoria J. Fraser, M.D., Katherine Haffenreffer, B.S., Eric Cui, B.S., Rebecca E. Kaganov, B.A., Karen Lolans, B.S., Jonathan B. Perlin, M.D., Ph.D., and Richard Platt, M.D., for the CDC Prevention Epicenters Program and the AHRQ DECIDE Network and Healthcare-Associated Infections Program*

C Bloodstream Infection from Any Pathogen



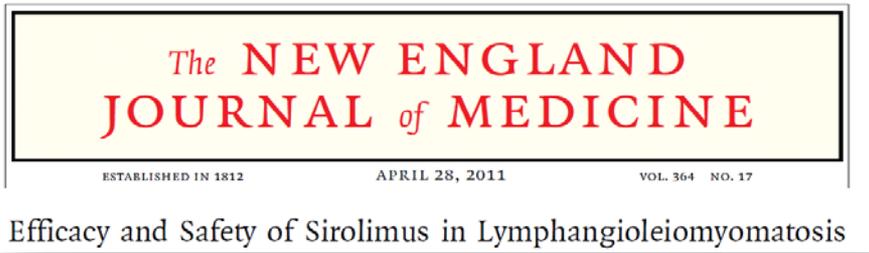
no prior experience in clinical research. Finally, the efficient design meant that the total cost of the trial, including the decolonizing product and contributed personnel effort, was less than \$3 million, or approximately \$40 per patient.

Another Disruptive Technology: Patients

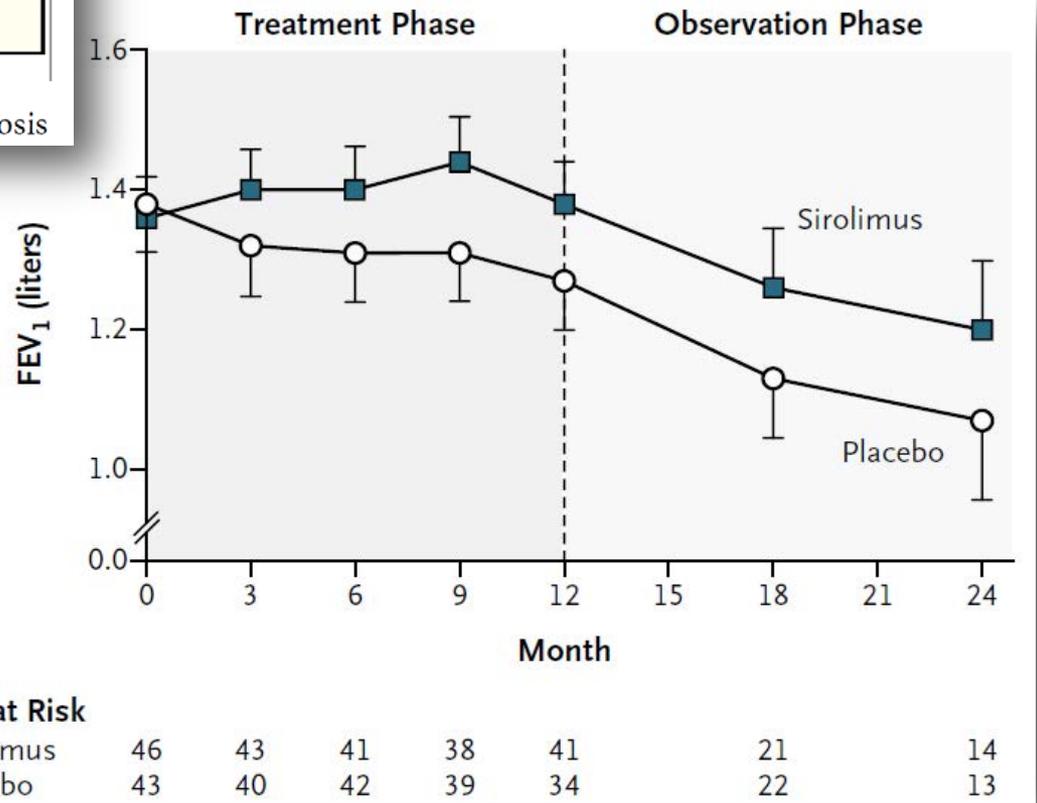


“The LAM Foundation urgently seeks safe and effective treatments, and ultimately a cure, for LAM through **advocacy and the funding of promising research**. We are dedicated to serving the scientific, medical and patient communities by offering information, resources and a worldwide network of hope and support.”

Lessons from a Rare Disease Trial



NIH Office of Rare Diseases
FDA
CIHR
Pfizer
Japanese MOH
LAM Foundation
Tuberous Sclerosis Alliance
Cincinnati Children's Hospital
Adler Foundation
NHLBI (DIR)



Improved QOL and functional performance (P=0.03 both)

What it Took...

EDITORIALS



Patient Organizations and Research on Rare Diseases

Julie R. Ingelfinger, M.D., and Jeffrey M. Drazen, M.D.

“This research study shows that when patients and researchers work together toward a common goal, advances can be made. The research community contributes ideas and investigative know-how, and patients who have the illness contribute their personal insights, biologic samples, and their time to prove principles. Most important, patients with such a rare disease are willing to put themselves at risk in order to find a treatment or a cure.”

Patient Engagement: Civic Obligation?

SPECIAL COMMUNICATION

The Obligation to Participate in Biomedical Research

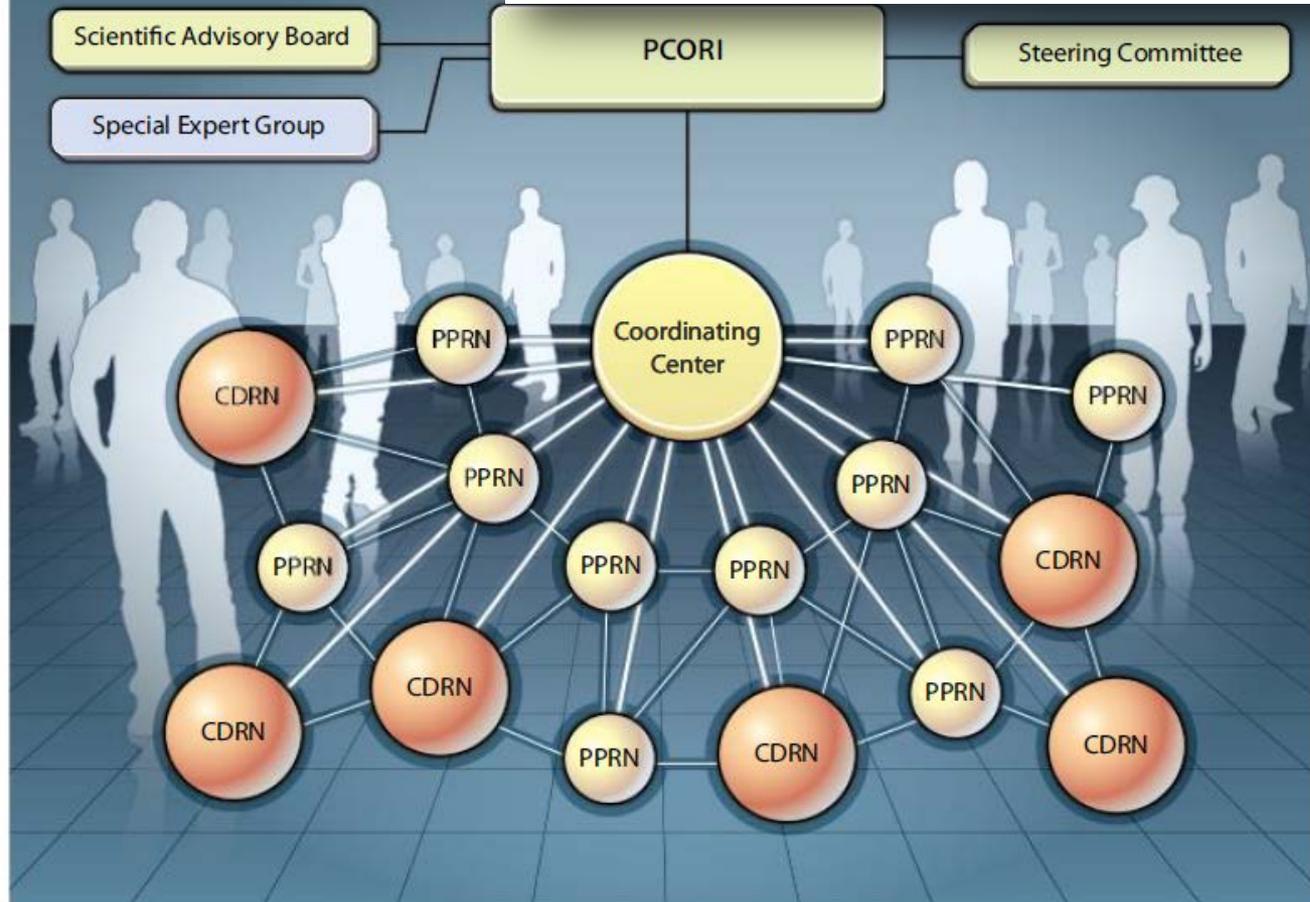
“Biomedical knowledge is a public good, available to any individual even if that individual does not contribute to it. Participation in research is a critical way to support an important public good. Consequently, all have a duty to participate. The public goods argument implies that individuals should participate unless they have a good reason not to. Such a shift would be of great aid to the progress of biomedical research, eventually making society significantly healthier.”

PCORI!

Network News: Powering Clinical Research

Joseph V. Selby,¹ Harlan M. Krumholz,^{2,3} Richard E. Kuntz,^{3,4}
Francis S. Collins^{3,5*}

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.



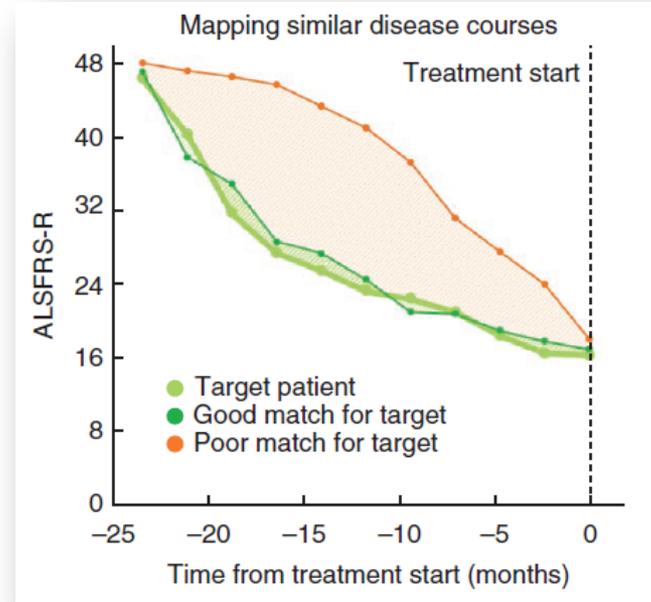
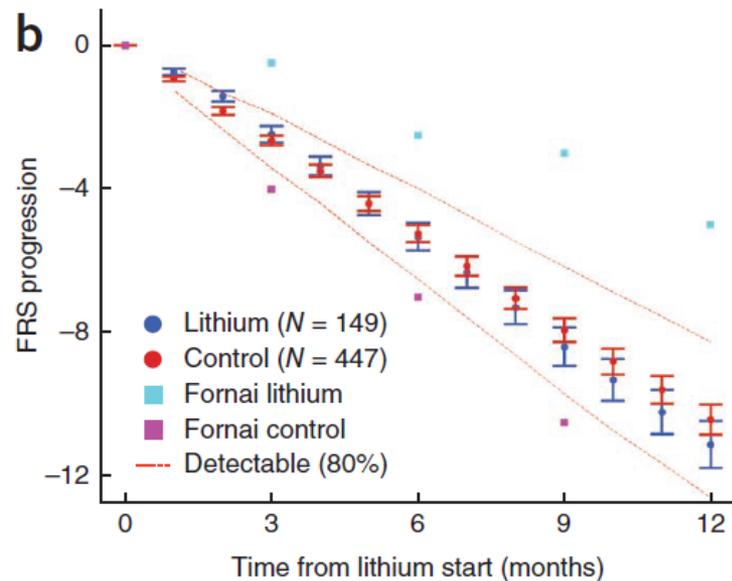
Patient-Initiated Internet Research

_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.”

Possible “New” Disruptive Models

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 to Win with Disruptive Technologies

Embed into existing projects

Create “small sub-organizations”

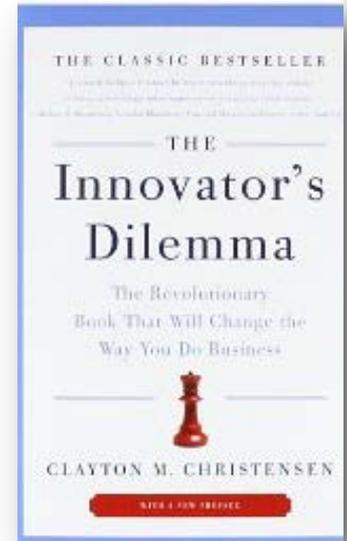
- Generate excitement
- Thrilled with “small wins”

Fail early, often, and inexpensively

Utilize resources, but not processes/values

Look for new markets, compete elsewhere

- Existing markets can mislead us





Notice of Intent to Publish a Funding Opportunity Announcement for Low-Cost Pragmatic Patient-Centered Randomized Controlled Intervention Trials (UH2/UH3)

Notice Number: NOT-HL-13-187

Key Dates

Release Date: August 1, 2013

Estimated Publication Date of Announcement: October 2013

First Estimated Application Due Date: January 2014

Earliest Estimated Award Date: September 2014

Earliest Estimated Start Date: September 2014

Issued by

National Heart, Lung, and Blood Institute ([NHLBI](#))

National Institute on Aging ([NIA](#))

National Institute on Deafness and Other Communication Disorders ([NIDCD](#))

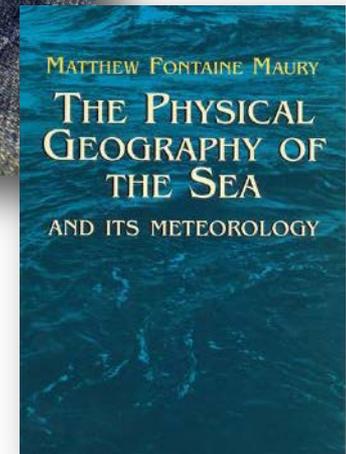
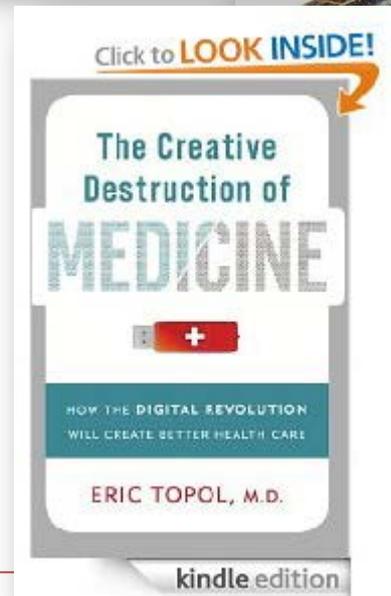
National Institute on Drug Abuse ([NIDA](#))

National Institute of Nursing Research ([NINR](#))

National Center for Complementary and Alternative Medicine ([NCCAM](#))

Models for Clinical, “Big-Data” Research

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





National Heart, Lung,
and Blood Institute