# Perspectives on Large Simple Trials

Michael S Lauer, MD, FACC, FAHA
Director, Division of Cardiovascular Sciences
NHLBI/NIH
May 8, 2012

Disclosures: None financial; my views only

National Heart Lung and Blood Institute

# Three Questions

- Why trials?
  - As opposed to observational studies
- Why large?
  - As opposed to small (or meta-analyses)
- Why simple?
  - As opposed to complex

# Hot Off the Press…


THE WALL STREET JOURNAL.


HEALTH INDUSTRY | Updated May 4, 2012, 10:24 p.m. ET

Analytical Trend Troubles Scientists

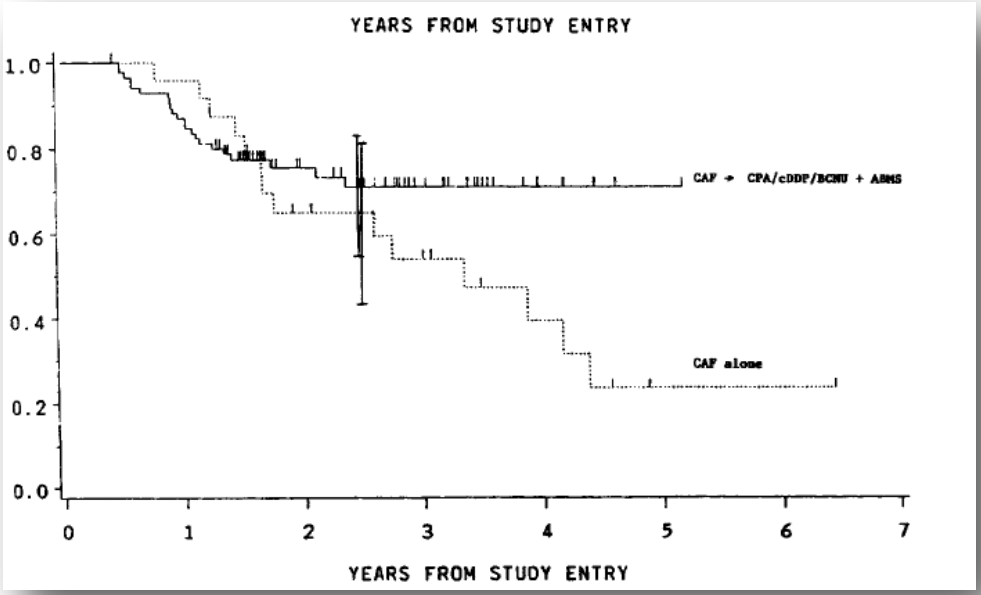
Article Comments (116)

While the gold standard is the randomly controlled experimental study, scientists have rushed to pursue observational studies, which are much easier, cheaper and quicker to do. Costs for a typical controlled trial can stretch high into the millions; observational studies can be performed for tens of thousands. … But observational studies are prone to methodological and statistical biases that can render the results unreliable. … Observational studies have never been more popular.



Naik G. Wall Street Journal May 4, 2012

# Not a New Problem…



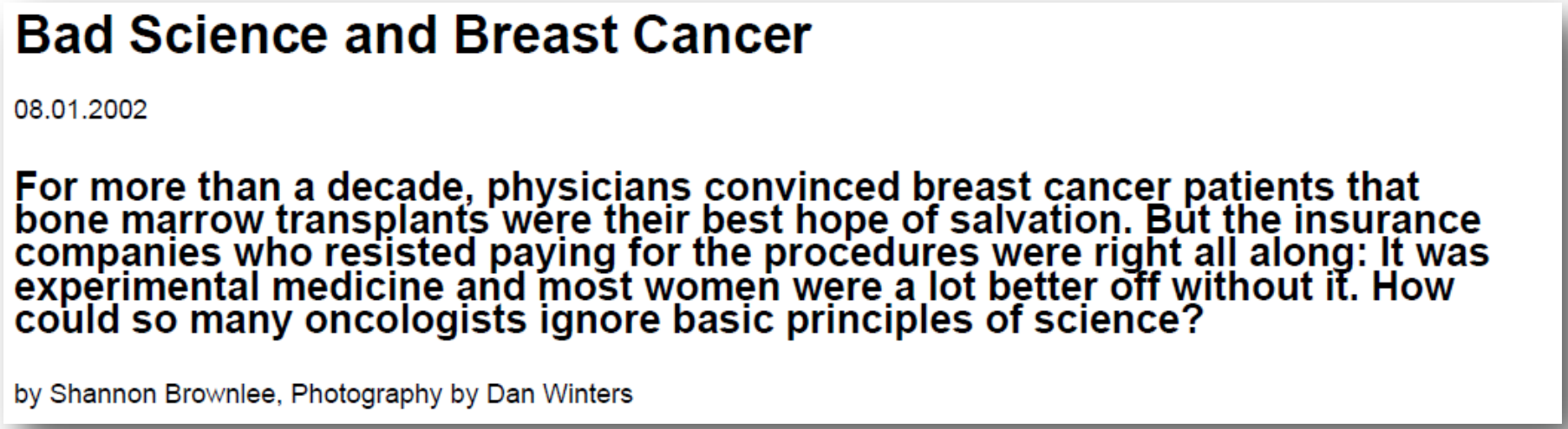

"…We believe that confirmation of these results in a prospective randomized trial is important before this therapy can be accepted for widespread use. Many new therapies, initially promising, fizzle. This treatment should only be offered at major centers…and, whenever possible, [into] randomized comparative trials…"



Peters WP, et al. J Clinical Oncology 1993;11:1132-43

National Heart Lung and Blood Institute

# What Actually Happened



**Bad Science and Breast Cancer**

08.01.2002

**For more than a decade, physicians convinced breast cancer patients that bone marrow transplants were their best hope of salvation. But the insurance companies who resisted paying for the procedures were right all along: It was experimental medicine and most women were a lot better off without it. How could so many oncologists ignore basic principles of science?**

by Shannon Brownlee, Photography by Dan Winters

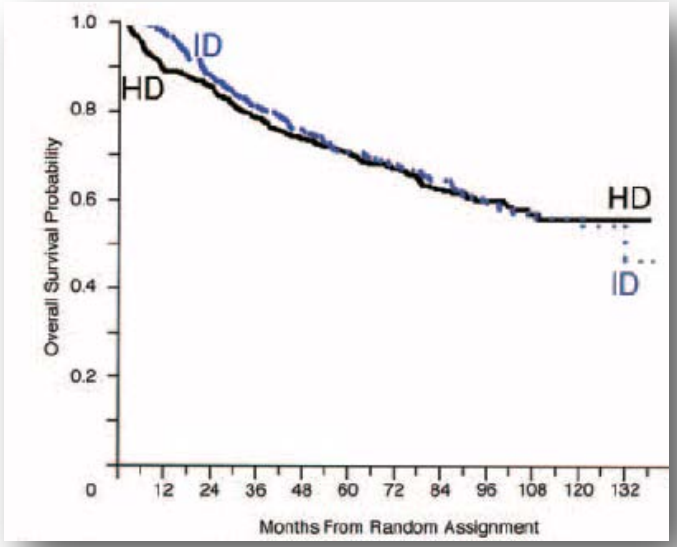
"… By the time Peters had organized his trial, few women wanted to participate…[It] meant running the risk of not getting high-dose chemo, and many had read newspaper accounts that convinced them that the treatment was their only chance for survival. **Their doctors often agreed.** One transplanter pulled out a copy of Peters' 1993 paper. 'I don't see how it's even *ethical* to do a randomized trial,' he said."

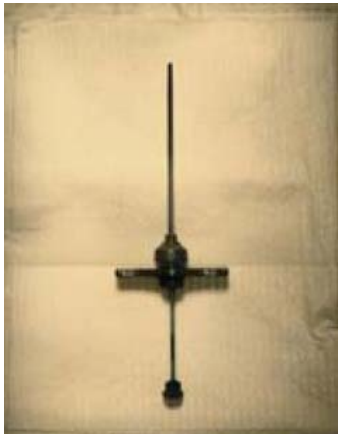


Brownlee S. Discover Magazine 2002.

# What Actually Happened; Large RCT

"… From the moment Peters first administered high-dose chemotherapy until the first clinical trials were concluded, nearly 20 years passed. During that time, hundreds of physicians practiced the unproven treatment. An estimated 30,000 breast cancer patients suffered through high-dose chemotherapy, **only a fraction of them as part of a clinical trial.** All told, the nation spent around $3 billion paying for it, while an estimated 4,000 to 9,000 women died not from their cancer but from the treatment…"





Brownlee S. Discover Magazine 2002.
Peters WP et al. J Clinical Oncology 2005;23:2191-2200

National Heart Lung and Blood Institute

# Another Story…

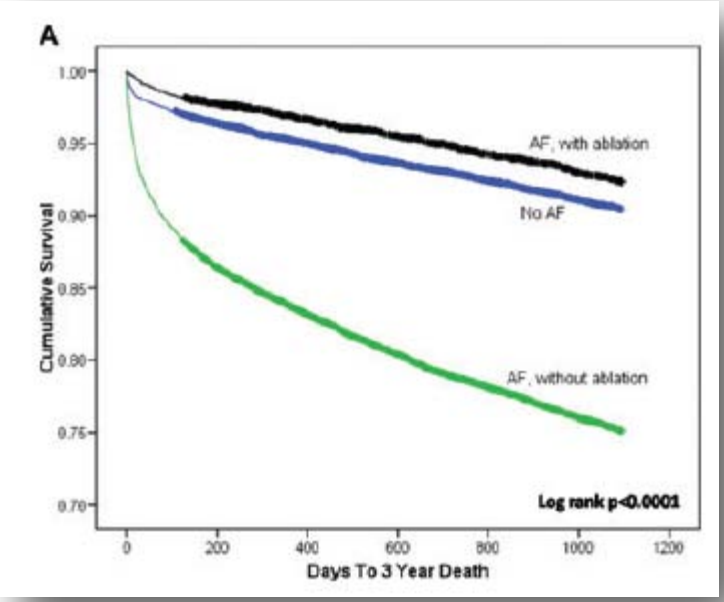
**Patients Treated with Catheter Ablation for Atrial Fibrillation Have Long-Term Rates of Death, Stroke, and Dementia Similar to Patients Without Atrial Fibrillation**

T. JARED BUNCH, M.D.,*,† BRIAN G. CRANDALL, M.D.,*,† J. PETER WEISS,*,† HEIDI T. MAY, PH.D., M.S.P.H.,† TAMI L. BAIR,† JEFFREY S. OSBORN, M.D.,*,† JEFFREY L. ANDERSON, M.D.,† JOSEPH B. MUHLESTEIN, M.D.,† BENJAMIN D. HORNE, PH.D., M.P.H.,† DONALD L. LAPPE, M.D.,† and JOHN D. DAY, M.D.*,†

From the *Intermountain Heart Rhythm Specialists, and †Department of Cardiology, Intermountain Medical Center, Murray, Utah, USA

**Conclusion**

In this system-wide study, the long-term outcomes after catheter ablation for AF are favorable. These favorable outcomes extend beyond rhythm control alone and appear to minimize the negative impact of AF on death, stroke, and dementia. These findings are in contrast to current pharmacologic therapies, which are limited long term by ineffectiveness and toxicity. These findings herald the need for randomized trials to evaluate these endpoints with catheter ablation to further understand mechanisms of benefit and to confirm these promising observational findings.



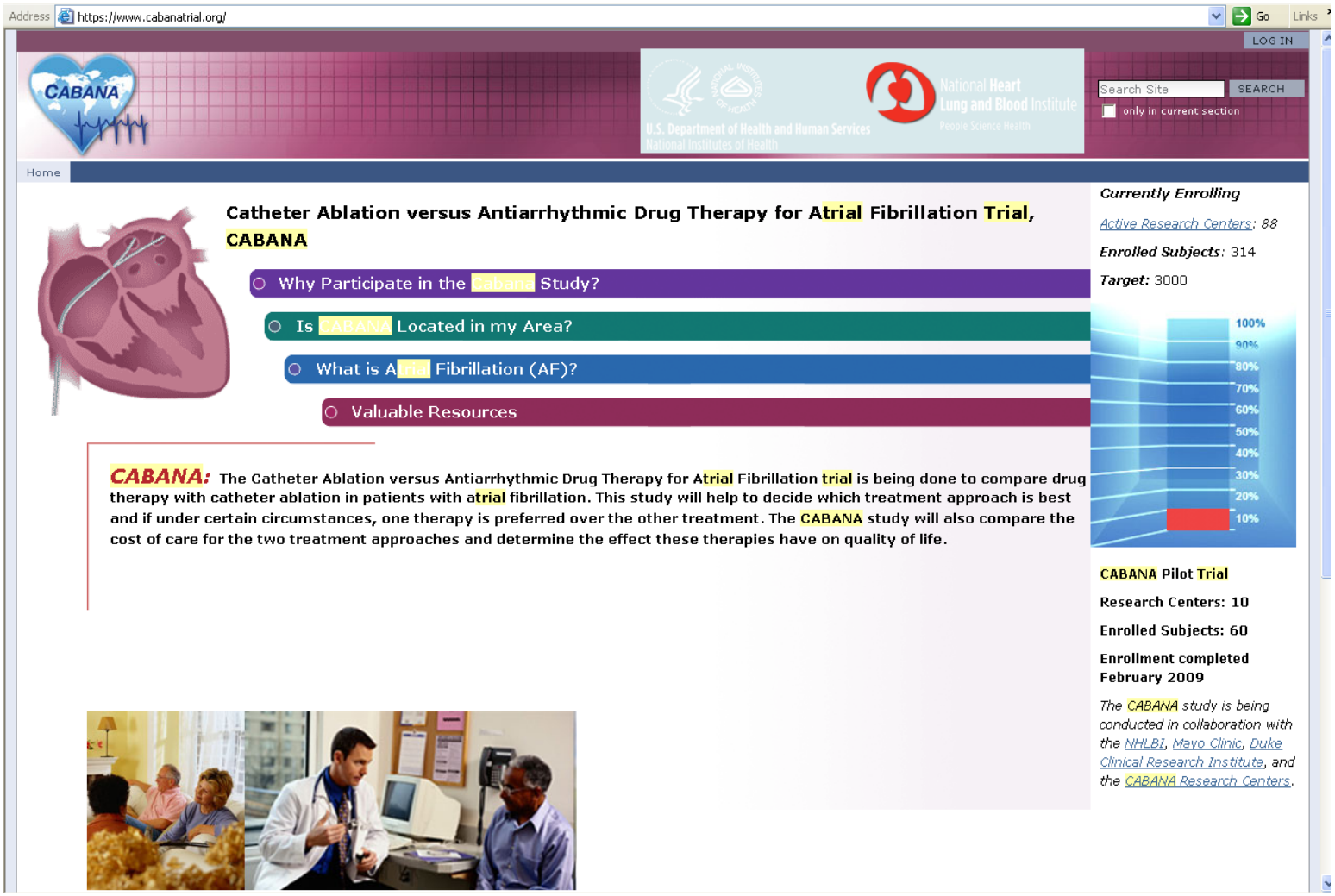

The paper: "These findings herald the need for randomized trials…to confirm these promising observational findings…"

The media: "Our studies shed light on the positive outcomes of catheter ablation… not only to reduce AF, but to …lower risk of suffering from a stroke or worse, loss of life."

 Bunch TJ et al. J CV Electrophysiol 2011; http://www.stopafib.org/newsitem...

National Heart Lung and Blood Institute

# We're Trying to Find the Answer…






National Heart Lung and Blood Institute

# Let's Look at These Stories

High-dose chemotherapy with ABMT

- Made sense
- Strong professional interest
  - Intellectual
  - Financial
- Observational data failed
- Stakeholders favored evidence-free medicine

Catheter ablation for atrial fibrillation

- Makes sense
- Strong professional interest: intellectual, financial
- Will stakeholders favor evidence-free medicine?

# Sometimes Observations Prove True

Lower blood pressure with drugs

Lower LDL cholesterol with statins

Aspirin to prevent MI and stroke

Beta-blockers and ACE inhibitors for CHF

Diagnostic tests:

- Mammography for breast cancer
- CT for lung cancer
- Ultrasound for abdominal aneurysm

# Sometimes not…

Vitamins to prevent cancer/CVD (failed)

Anti-arrhythmic drugs (higher death rate)

Hormone therapy (breast cancer, failed CHD)

Back surgery, kyphoplasty (little benefit)

Aggressive glucose reduction to prevent MI

Stents *after* myocardial infarction

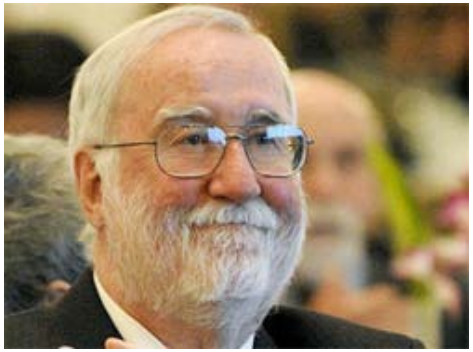
Bone marrow transplantation for breast cancer (higher death rate)



Thank you to Andrew Epstein

# It Boils Down to Fundamentals…

We cannot trust observational data to draw conclusions…



"It was because they were brilliant observers of humans, ***not experimenters*** upon them, and observation by itself provides insufficient evidence of the value of a treatment."

David Sackett

"The principle of science, the definition, almost, is the following: The test of all knowledge is the experiment. **Experiment is the sole judge of truth**."

Richard Feynman



With thanks to Robert Califf and David Sackett

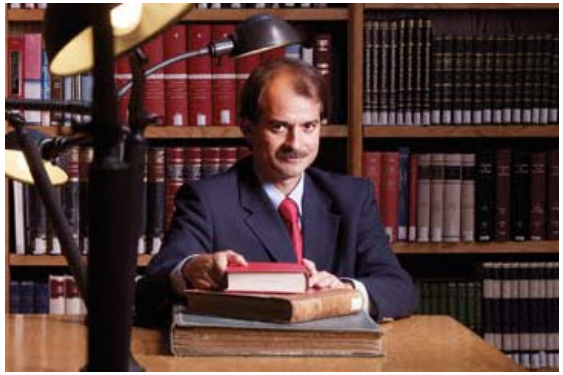
National Heart Lung and Blood Institute

# Why Large and Simple…

Essay

## Why Most Published Research Findings Are False

John P. A. Ioannidis



It can be proven that most claimed research findings are false.

"The smaller the studies conducted in a scientific field, the less likely the research findings are to be true."

The greater the flexibility in designs, outcomes, and analytical modes…the less like the findings are to be true."



Ioannidis JPA. PLoS Medicine 2005;2:e124

# Likelihood of Truth

| Design | Likelihood of Truth |
|---|---|
| Large, adequately powered RCT with little bias and 1:1 pre-study odds | 85% |
| Meta-analysis of small trials | 41% |
| Small, well-performed phase II trial | 23% |
| Large epidemiological study | 20% |
| Discovery-oriented exploratory research | 0.1% |



Ioannidis JPA. PLoS Medicine 2005;2:e124

# Remembering How to Do Simple Trials

**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

National Heart Lung and Blood Institute

# Simple (…and Often Pragmatic)

**Pragmatic**

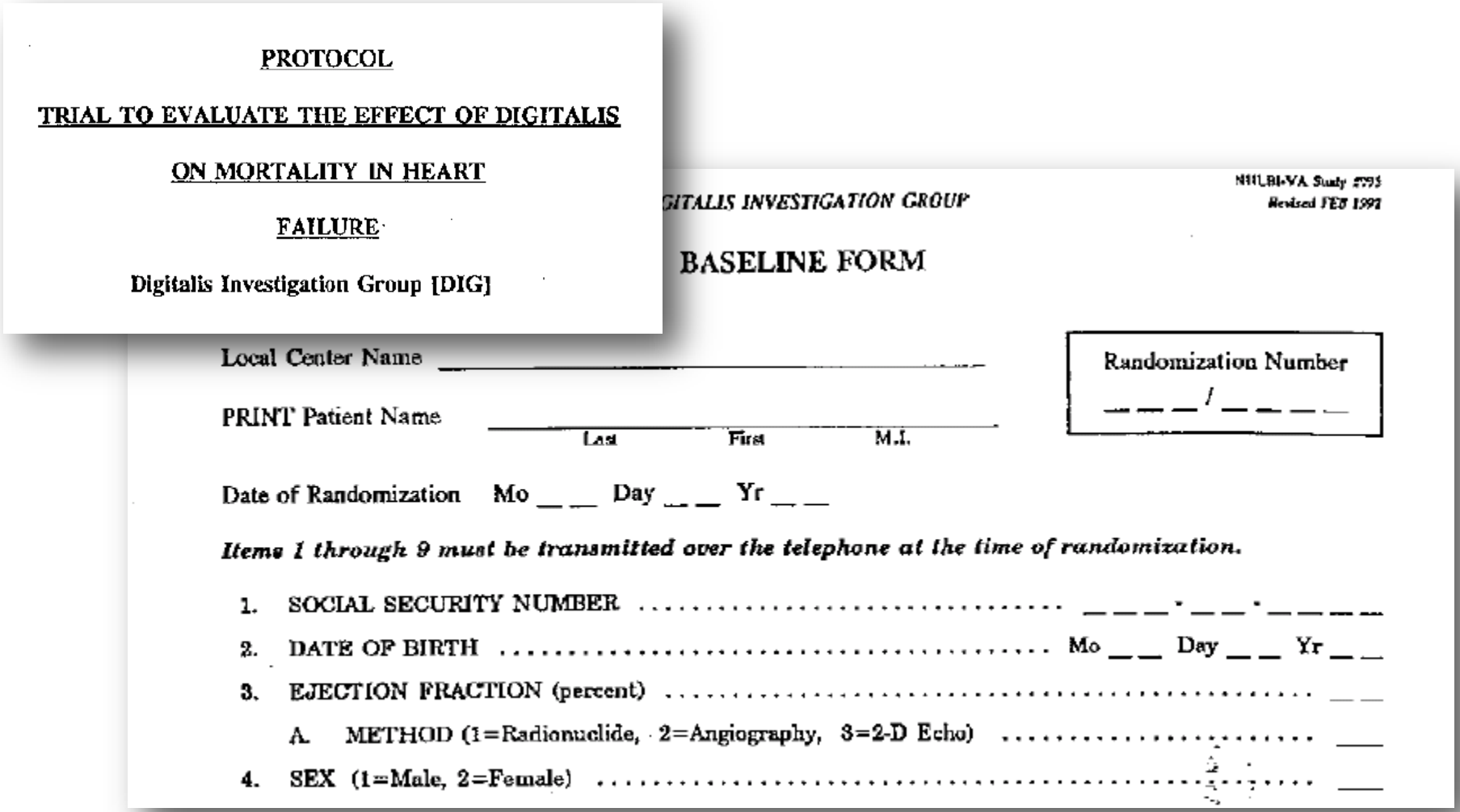
- Broad eligibility
- Flexible interventions
- Typical practitioners
- No follow-up visits
- Objective clinical outcome
- Usual compliance
- Intent-to-treat

**Explanatory**

- Narrow eligibility
- Strict instructions
- Expert practitioners
- Frequent follow-up visits
- Surrogate outcomes
- Close monitoring
- ITT plus per protocol


Thorpe KE et al. J Clin Epidemiol 2009;62:464-75

# Simple Trials in the United States



PROTOCOL

TRIAL TO EVALUATE THE EFFECT OF DIGITALIS

ON MORTALITY IN HEART

FAILURE

Digitalis Investigation Group [DIG]

GITALIS INVESTIGATION GROUP

NHLBI-VA Study 2795
Revised FEB 1992

BASELINE FORM

Local Center Name _____

PRINT Patient Name _____
Last First M.I.

Randomization Number
_ _ _ / _ _ _ _

Date of Randomization Mo _ _ Day _ _ Yr _ _

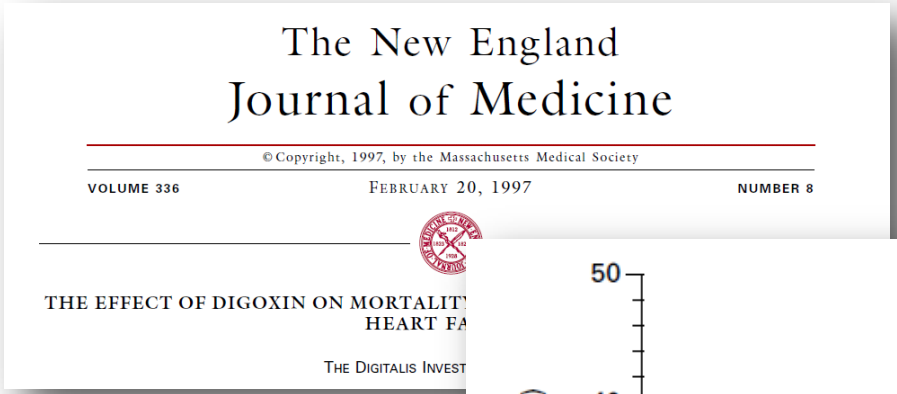
*Items 1 through 9 must be transmitted over the telephone at the time of randomization.*

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) ..... _



National Heart Lung and Blood Institute

# Robust Findings


The New England
Journal of Medicine

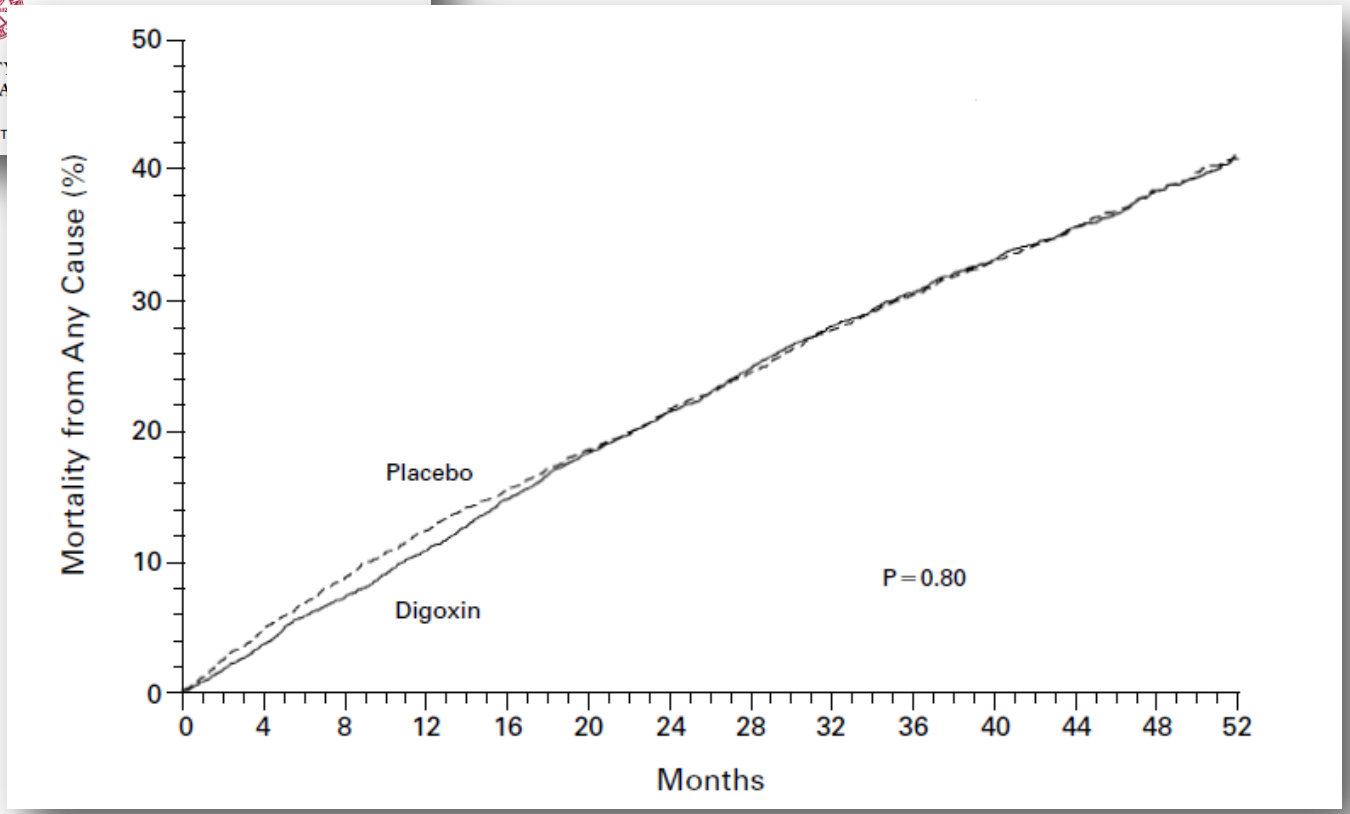


VOLUME 336 FEBRUARY 20, 1997 NUMBER 8

THE EFFECT OF DIGOXIN ON MORTALIT
HEART FA

THE DIGITALIS INVEST

N = 6800
HR = 0.99, 95% 0.91 – 1. 07




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

National Heart Lung and Blood Institute

# New Construct: Clinical Registry Trial

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

JAMA®

**Use of Continuous Quality Improvement to Increase Use of Process Measures in Patients Undergoing Coronary Artery Bypass Graft Surgery**

A Randomized Controlled Trial



Am Heart J 2010;160:1042-8; JAMA 2003;290:49-56

National Heart Lung and Blood Institute

# Why We Need New Business Models

EDITORIAL

## A Threat to Medical Innovation

Michael Rosbash is an Investigator of the Howard Hughes Medical Institute

THESE ARE DIFFICULT TIMES FOR THE U.S. NATIONAL INSTITUTES OF HEALTH (NIH). ITS 2011 BUDGET is 1% less than in 2010, and it is increasingly common for NIH to administratively decrease the size of awards across the board, before money goes out the door. The federal stimulus package buffered the impact of NIH budget issues. For example, approximately 36% of NIH grant

In the spirit of "never waste a good crisis," a serious evaluation of many NIH extramural policies and programs is warranted. They include expensive clinical and epidemiological research. Although long-standing constituencies make it hard to consider ending or even reducing these programs, their cost/benefit ratios should be honestly examined.



Rosbash M. Science 2011;333:136.

National Heart Lung and Blood Institute

# When Resources Are Scarce…

zipcar®
wheels when you want them

SOUTHWEST AIRLINES

FedEx®

ING



National Heart Lung and Blood Institute

# Four Questions

- Why trials?
  - To get the right answers
- Why large?
  - To get the right (robust) answers
- Why simple?
  - To get the right (practical, relevant) answers
- How?
  - Force a change in business models
  - Options: cluster, adaptive, clinical registry…