Perspectives on Large Simple Trials

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Disclosures: None financial; my views only
Three Questions

• Why trials?
  ▪ As opposed to observational studies

• Why large?
  ▪ As opposed to small (or meta-analyses)

• Why simple?
  ▪ As opposed to complex
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.
“...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...”

“... 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.”
“… 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…”

Peters WP et al. J Clinical Oncology 2005;23:2191-2200
Another Story…

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...
We’re Trying to Find the Answer…

Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial, CABANA

- Why Participate in the CABANA Study?
- Is CABANA Located in my Area?
- What is Atrial Fibrillation (AF)?
- Valuable Resources

CABANA: The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation trial is being done to compare drug therapy with catheter ablation in patients with atrial fibrillation. This study will help to decide which treatment approach is best and if under certain circumstances, one therapy is preferred over the other treatment. The CABANA study will also compare the cost of care for the two treatment approaches and determine the effect those therapies have on quality of life.

CABANA Pilot Trial
- Research Centers: 10
- Enrolled Subjects: 60
- Enrollment completed February 2009

The CABANA study is being conducted in collaboration with the NHLBI, Mayo Clinic, Duke Clinical Research Institute, and the CABANA Research Centers.
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 \textit{after} myocardial infarction
Bone marrow transplantation for breast cancer (higher death rate)
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
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.”

## Likelihood of Truth

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

“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
<table>
<thead>
<tr>
<th>Pragmatic</th>
<th>Explanatory</th>
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<tbody>
<tr>
<td>Broad eligibility</td>
<td>Narrow eligibility</td>
</tr>
<tr>
<td>Flexible interventions</td>
<td>Strict instructions</td>
</tr>
<tr>
<td>Typical practitioners</td>
<td>Expert practitioners</td>
</tr>
<tr>
<td>No follow-up visits</td>
<td>Frequent follow-up visits</td>
</tr>
<tr>
<td>Objective clinical outcome</td>
<td>Surrogate outcomes</td>
</tr>
<tr>
<td>Usual compliance</td>
<td>Close monitoring</td>
</tr>
<tr>
<td>Intent-to-treat</td>
<td>ITT plus per protocol</td>
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PROTOCOL

TRIAL TO EVALUATE THE EFFECT OF DIGITALIS
ON MORTALITY IN HEART FAILURE.

Digitalis Investigation Group [DIG]

BASELINE FORM

Local Center Name ________________________________

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=Radiouclide, 2=Angiography, 3=2-D Echo) ______
   4. SEX (1=Male, 2=Female) ____________________________
Robust Findings

N = 6800
HR = 0.99, 95% 0.91 – 1.07

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, 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

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
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.
When Resources Are Scarce…
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…