Randomized Controlled Trials vs. Observational Studies: The Next Great Debate in CER

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Let’s get ready to rumble...!

Experimental
Non-experimental

CER is Like the Blind Men and the Elephant

It’s a RCT!
It’s a meta-analysis!
It’s a model!
It’s an observational study!

What is this?!
All of the above?

CER is Like the Blind Men and the Elephant

It’s a RCT!
...but not a confounded observational study!
It’s an observational study!

...but not an artificial RCT!

Can’t We (Different Study Types) Just Get Along?

“Experiment, observation, and mathematics, individually and collectively, have a crucial role in providing the evidential basis for modern therapeutics. Arguments about the relative importance of each are an unnecessary distraction. Hierarchies of evidence should be replaced by accepting - indeed embracing - a diversity of approaches.”

- Sir Michael Rawlins, head, NICE, Lancet 2008
Randomized Trials Vs. Observational Studies

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May 22, 2011

Disclosures: None financial; my views only

A True Story

“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…”


What Actually Happened

Bad Science and Breast Cancer

“… 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.”


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…”

Peters WP et al. J Clinical Oncology 2005;23:2191-2200
Hot Off the Press…

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.”

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 the 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)

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
The Fundamentals...

Failure to account for unmeasured (or improperly measured) confounders

Failure to abide by the intent-to-treat principle
“*If you do not ask the right questions, you do not get the right answer.*”
--- Edward Hodnett


Another Fundamental…Effect Size

"Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials"

Gordon CS Smith, JBP Patel

Conclusions: As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence-based medicine have criticized the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence-based medicine organized and participated in a double-blind, randomized, placebo-controlled, crossover trial of the parachute.

Smith GCS, Pell JP. BMJ 2003;327:1459-61

Illustration of Fundamentals...

Essay

Why Most Published Research Findings Are False


“The greater the financial interests and prejudices, the less likely the research findings are to be true. (Excess bias)

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

Likelihood of Truth

- Design
  - 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%

With Humility It Can Be Done: Marfan

“*The National Marfan Foundation does not recommend switching from a beta blocker to losartan as a way to manage Marfan syndrome until the trial is completed.* This is because we do not know whether losartan is clearly better than atenolol for taking care of people with Marfan syndrome. Also, we do not know if people with Marfan syndrome will have unwanted side effects when they take losartan.”

http://www.marfan.org/marfan/2408/Atenolol-vs-Losartan-Clinical-Trial

Marshall E. Science 2008;320:600-3 and 2010;330:900-1
Final Thoughts

Lessons of history
- Many (deadly) failures
- Trapped by hype, hope, and real conflicts
- Some (high-impact) successes

Lessons of science: fundamentals
- Unmeasured confounders
- Failure to abide by intent-to-treat
- Failure to appreciate impact of effect size

Appropriate Roles for Observational Studies

Determine the need for RCT
- Generate hypotheses
- Identify extreme effect sizes
  - Unusual safety signals
  - Rare therapies (e.g. antibiotics in pneumonia)

After the RCT
- Extend findings to “real world”
- Evaluate dissemination and impact

Pragmatic Clinical Trials vs Observational Studies: Choose the Right Method to Answer the Right Comparative Effectiveness Questions Efficiently
Choice of Study Designs for Comparative Effectiveness Research

- Retrospective Observational Study
- Prospective Observational Study
- Naturalistic Randomized Clinical (Pragmatic) Trial
- Randomized Clinical Trial (RCT)

<table>
<thead>
<tr>
<th>Term</th>
<th>Efficacy</th>
<th>Relative Efficacy</th>
<th>Effectiveness</th>
<th>Relative Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Extent to which an intervention does more harm than good...</td>
<td>under ideal circumstances</td>
<td>compared to one or more alternative interventions</td>
<td>when provided under the usual circumstances of health care practice</td>
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<td>Key Features</td>
<td>Randomization (typically select patients recruited from high volume centers)</td>
<td>Randomization</td>
<td>Observational</td>
<td>• Observational  • Naturalistic PCT</td>
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The Role of Private Industry in Pragmatic Comparative Effectiveness Trials

Don P. Buesching, PhD; Bryan R. Luce, PhD; Marc L. Berger, MD (submitted for publication)

- Literature review of industry-sponsored PCTs published/reported from 1996 to 2010
- 9 PCTs (8 chronic, 1 acute care)
  - Naturalistic, Head-to-head vs standard of care or similar agents; 2 included “usual care” arm
  - Chronic care trial length averaged 12 (range 6 to 24) months
  - Six (all chronic care) studies reported equivocal or no difference in effectiveness between comparators
  - 2 of 8 chronic and 1 of 1 acute care PCTs favored sponsor product.
- Lack of difference in most studies impacted by “typical practice,” i.e. treatment switching (rapid, complex)
- In one study, could distinguish contribution of initial treatment through statistical adjustment (ex. Fixed epoch and marginal structural modeling)

CAUTION!

RANDOMIZATION IS NOT A PANACEA
Making the Question Clear, Getting the Question Right

- What happens if everyone in a given population were exposed to treatment vs an alternative?
  - Initial Care Strategy
  - Target Population is Whole Population
  - Average Causal Effect

- What happens to only those who actually receive treatment?
  - Effectiveness of treatment
  - Target Population is Typically Treated Population
  - Local Causal Effect

- What happens to only those who actually use the treatment?
  - Upper limit of effectiveness of treatment (minimal difference between efficacy and effectiveness)
  - Target Population is Actually Treated Population

- What happens to particular patient subsets (ex. elderly patients with certain comorbidities)
  - Subsets that may have been excluded from RCTs
  - Target Population is Patient with specific characteristics (Subpopulation)

Conclusions

- Comparative Effectiveness Research is difficult. To answer the policy questions we want answered in an efficient fashion, we must deploy the full array of study design choices

- RCTs will always be necessary – but will not provide information on effectiveness, and it is infeasible to expect that all desired RCTs will be feasible, funded, and timely

- Judicious use of naturalistic PCTs and observational studies that follow good research practices are needed to supplement results from RCTs

- Observational studies are a key component of a “learning health care system”

- To leverage observational studies for health policy decisions, it is critical that the study question is clear and relevant

- There is work to be done in learning how to best design PCTs such that they provide the most relevant CE information

Thank You!