The Use of Large, Simple Trials to Answer Comparative Effectiveness Research and Safety Questions

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Contents

Background, Definition, Design

Large Simple Trials in the Context of Healthcare Decision Making

A Look Back at Large Simple Trials

The Future for Large Simple Trials?
Background, Definition, Design
The Research Imperative

“Worldwide, hundreds of thousands of premature deaths a year could be avoided by seeking large-scale randomized evidence... appropriately large-scale randomized evidence could vastly improve the management of many important, but non-fatal, medical problems.”

Definition

**Large**
- > 1000 patients
- To be able to show moderate but worthwhile benefits

**Simple**
- Streamlined Entry criteria
- Treatments
- Data requirements
- To enable the practical delivery of such large studies

**Trial**
- Randomization
- Minimize occurrence of bias
- Promotes research validity
Large Simple Trials Combine Observational and Experimental Design Features

- **Experimental**
  - Patient randomization
  - Strongest Internal Validity

- **Large Simple Trial**

- **Observational**
  - Usual care settings & patient management
  - Strongest External Validity
Large Simple Trials Fall towards the Pragmatic End of the Experimental Trial Design Spectrum

- Measure Effectiveness
  - Determine the effects of an intervention under the usual conditions in which it will be applied

- Measure Efficacy
  - Determine the effects of an intervention under ideal circumstances
Ten Ways in Which Pragmatic and Explanatory Trials Can Differ

- Participant eligibility criteria
- Flexibility of experimental intervention
- Practitioner expertise (experimental intervention)
- Flexibility of the comparison intervention
- Practitioner expertise (comparison intervention)
- Follow-up intensity
- Primary trial outcome
- Participant compliance with “prescribed intervention”
- Practitioner adherence to study protocol
- Analysis of primary outcome

Thorpe et al 2009 CMAJ:180(10)
Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)

- Practitioner expertise (experimental)
- Flexibility of experimental intervention
- Eligibility criteria
- Primary analysis
- Practitioner adherence
- Outcomes
- Follow-up intensity
- Practitioner expertise (comparison)
- Flexibility of the comparison intervention
- Participant compliance

Thorpe et al 2009 CMAJ:180(10)
Mapping Explanatory Randomized Clinical Trials

Explanatory Randomized Clinical Trials

- Practitioner expertise (experimental)
- Flexibility of experimental intervention
- Eligibility criteria
- Primary analysis
- Practitioner adherence
- Outcomes
- Participant compliance
- Follow-up intensity
- Flexibility of the comparison intervention
- Practitioner expertise (comparison)

Thorpe et al 2009 CMAJ:180(10)
Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)

Thorpe et al 2009
CMAJ:180(10) Large Simple Trials
Large Simple Trials in the Context of Healthcare Decision Making
Evidence for Healthcare Decision Making

- Audits or Surveys
- Case Control Studies
- Administrative Databases
- Efficacy Trials
- Registries
- Systematic Reviews and Meta-analyses
- Effectiveness Trials including LSTs
- Cohort Studies
- Audits or Surveys
- Case Control Studies
- Administrative Databases
- Efficacy Trials
- Registries
- Systematic Reviews and Meta-analyses
- Effectiveness Trials including LSTs
- Cohort Studies

Adapted from Atkins D., Medical Care;45:10(2) S16
Evaluating the Evidence from the Decision Maker Perspective

Adapted from Atkins D., Medical Care;45:10(2) S16
When Should the LST Design Methodology be Chosen?

<table>
<thead>
<tr>
<th>Should be considered when:</th>
<th>Alternatives include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Objective is to demonstrate comparative effectiveness/safety in “real-world”</td>
<td>• Other types of Pragmatic Phase IV RCT</td>
</tr>
<tr>
<td>• Randomization is required to avoid confounding</td>
<td>• Purely observational (non-randomized) study</td>
</tr>
<tr>
<td>• Endpoints can be evaluated through (largely) observational follow-up</td>
<td>• Non-randomized prospective study with scheduled follow-up and endpoint collection</td>
</tr>
<tr>
<td>• A large sample size is needed to demonstrate moderate but clinically relevant treatment effects</td>
<td></td>
</tr>
</tbody>
</table>
A Look Back at Large Simple Trials to answer Comparative Effectiveness and Safety Questions
Identifying Large Simple Trials

– clinicaltrials.gov and literature search
– ~40 Large Simple Trials
– LSTs less than 0.04% of over 98,000 trials in clinicaltrials.gov

– Limitations:
  • Data pre-2000
  • Breadth of information available (objective, monitoring strategies etc)
Trends in LSTs since 2000

Indications are that the number of LSTs are trending upwards from 12 (2000 – 2004) to 21 (2005 – 2009)
Therapeutic Focus

Cardiovascular Disease
## Motivations

Majority evaluate both safety and efficacy endpoints

<table>
<thead>
<tr>
<th>Endpoint Classification*</th>
<th># LSTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>5</td>
</tr>
<tr>
<td>Efficacy</td>
<td>8</td>
</tr>
<tr>
<td>Safety/Efficacy</td>
<td>24</td>
</tr>
</tbody>
</table>

*clinicaltrials.gov
Examples of Large Simple Trials

GISSI  ALLHAT  CATIE
ISIS    REALITY  PERSPECTIVE
COPE    SMART    ZODIAC
Case Studies
Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto (GISSI)

GISSI Trials in Acute Myocardial Infarction (MI)
Aldo P. Maggioni, Maria G. Franzosi, Claudio Fresco, Fabio Turazza and Gianni Tognoni
Chest 1990;97;146S-150S

Overview:
• 176 Coronary Care Units
• 12,000 Patients
• 6 month FU for clinical events over 15 month period
• Budget $400,000
• Core organizational group of investigators and support staff

Results:
The GISSI studies showed striking evidence of the effectiveness and safety of intravenous thrombolytic treatment in acute MI. Nearly all Italian CCUs took part, so the results were highly representative. The package of treatments recommended from the study data was widely adopted, and led to a dramatic reduction in the overall mortality of Italian patients with acute MI.
The Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group.
JAMA. 2002; 288:2981:2997

Overview:
• Compared clorthalidone, lisonopril, amlodipine, and doxazosin
• Over 42,000 Patients with significant representation
• Eight year duration
• Budget over $100M funded by NIH

Results:
ALLHAT was ambitious but the results were hotly debated; there were design problems. Meta-analyses and other large trials suggested different answers. ALLHAT was outpaced by medical science with evolution in the treatment of hypertension and hyperlipidemia, making the original research questions outdated.
The Future for Large Simple Trials?
Early-stage RCT may fail to demonstrate full efficacy, or costs may be too high. With the rush to bring new drugs to market to address patient needs or capture market share, demonstrated value of the drug can be less than transparent.
Coverage with Evidence Development (CED) links Medicare coverage of specific promising technologies to a requirement that the patients participate in a registry or clinical trial.

### Select CED Cases, 2003-2010

<table>
<thead>
<tr>
<th>Technology</th>
<th>Year</th>
<th>Notes</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer vaccine</td>
<td>2010</td>
<td>CMS to determine whether coverage is “reasonable and necessary” for prostate cancer patients. One treatment is nearly $93,000.</td>
<td>Review ongoing</td>
</tr>
<tr>
<td>Home use of oxygen</td>
<td>2006</td>
<td>CMS expands coverage for home use of oxygen to less severely impaired patients enrolled in RCT</td>
<td>Trials under way</td>
</tr>
<tr>
<td>Cochlear implantation</td>
<td>2005</td>
<td>CMS expands coverage for patients with less severe hearing loss based on enrollment in RCT</td>
<td>No proposals for trials in response to NCD</td>
</tr>
<tr>
<td>Chemotherapy for colorectal cancer</td>
<td>2005</td>
<td>CMS covers off-label use of chemotherapy drugs for patients enrolled in NCI-sponsored RCTs</td>
<td>NCI trials ongoing</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillators</td>
<td>2005</td>
<td>CMS covers ICDs for subgroup</td>
<td>Registry ongoing</td>
</tr>
<tr>
<td>PET for cancers</td>
<td>2005</td>
<td>CMS expands coverage of PET for cancer to situations where providers and patients are enrolled in prospective data collection system</td>
<td>Trials ongoing</td>
</tr>
<tr>
<td>PET for suspected dementia</td>
<td>2004</td>
<td>CMS covers FDG-PET for patients enrolled in a “large practical clinical trial”</td>
<td>NCI trials ongoing</td>
</tr>
<tr>
<td>Lung volume reduction surgery</td>
<td>2003</td>
<td>CMS covers LVRS only for patients who benefit and only in approved facilities</td>
<td>Trial published in 2003, use of LVRS falls after trial</td>
</tr>
</tbody>
</table>
Rising health care expenditures exceeding $2.2 trillion, or 16% of GDP, are impetus for federal health care reform policies

The American Recovery and Reinvestment Act of 2009 appropriated $1.1B for CER out of the $787.2 Congressional Economic Stimulus Bill

IOM recommended CER review of the top 100 topics most important to the health of the US population

Source: IOM report 2009
Institute of Medicine (IOM) Comparative Effectiveness Priorities

- Many of the LSTs conducted in the past are aligned with the IOM list of priorities.
- However, about 85% of studies producing comparative effectiveness research are non-randomized*
- Observational research methods are evolving and studies can provide highly meaningful data if carefully designed
- LSTs offer a strong methodological approach to CER but structure and affordability must be addressed

*Holve & Pittman, Academy Health, 2009
Decision Makers want Better Evidence

Comparative Effectiveness Research

Robert J. Temple, M.D. Deputy Center Director for Clinical Science Center for Drug Evaluation and Research U.S. Food and Drug Administration

FDA/DIA Statistics Forum April 21, 2010

CDER Recommends:
“Doing large studies in treatment environments already collecting data (HMO’s, VA), perhaps using internet to enrol, gain consent, follow PRO outcomes. These would not select too much, i.e., were talking about very pragmatic trials.”
The Future for Large Simple Trials?

- Cost
- Organization
- Sponsorship

Healthcare stakeholders
Design approaches & analytical techniques
Data access & linkage