Pragmatic Trials

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Outline

- Overview—What are Pragmatic Trials (PTs)? Why are They Important?
- How are PTs Different than Explanatory Trials?
- An example: Be Fit Be Well Study
- Comparison/Control Conditions in PT
- PRECIS Criteria
- Summary and Discussion
Definitions

• A pragmatic (or practical) trial seeks to answer the question, “Does an intervention work under usual conditions?”

• An explanatory (or efficacy) trial seeks to answer the question, “Can an intervention work under ideal conditions?”
Why are Pragmatic Trials Needed?

We are:

• Not reaching patients with complex, comorbid problems and those most in need
• Not testing in settings and with staff that are typical to most clinical situations
• Not addressing issues important to clinicians, policy makers, and patients
• Many “evidence-based” interventions are not feasible in most real-world settings
• Bottom Line—Research not seen as RELEVANT

Rothwell, P. M. Lancet, 2005;365, 82-93.
Pragmatic Trials: Key Contextual Characteristics

- Questions from, and important to, stakeholders
- Multiple, heterogeneous settings (and staff)
- Representative populations
- Comparison conditions are real-world alternatives
- Multiple outcomes important to decision and policy makers

Thorpe KE et al., Can Med Assoc J, 2009, 180: E47-57
Tunis SR et al. Practical clinical trials...JAMA 2003;290:1624-1632
Glasgow RE et al. Practical clinical trials...Med Care2005;43(6):551-557
## Explanatory vs. Pragmatic Design Features for a Medication Adherence Trial

<table>
<thead>
<tr>
<th>Design decision</th>
<th>Explanatory</th>
<th>Pragmatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which clinics to approach?</td>
<td>Highly motivated site(s) within high performing systems having excellent EMR resources</td>
<td>Randomly selected site(s) from multiple, diverse delivery systems</td>
</tr>
<tr>
<td>Which clinicians to approach?</td>
<td>Highly motivated clinicians within those sites</td>
<td>All clinicians within those sites</td>
</tr>
<tr>
<td>Which patients to enroll?</td>
<td>Highly motivated patients with minimal comorbidity</td>
<td>All patients newly prescribed a statin, regardless of comorbid physical or psychosocial problems</td>
</tr>
<tr>
<td>What level of comfort with cell phones to select for?</td>
<td>Comfortable using wide range of cell-phone features</td>
<td>No cell phone (need to provide one and instruct), or wide range of comfort with cell-phone features</td>
</tr>
<tr>
<td>How frequently to send text messages?</td>
<td>Frequently; isolated from workflow in clinic, close highly individualized intensive monitoring</td>
<td>Less frequently, but consistent with workflow patterns in clinic</td>
</tr>
<tr>
<td>What level of training to require from supporting clinical pharmacist?</td>
<td>Single individual, highly experienced, trained in motivational interviewing</td>
<td>Multiple clinical pharmacists with standard training in patient counseling</td>
</tr>
<tr>
<td>What kind of advice protocol to provide?</td>
<td>Highly scripted, standardized</td>
<td>Unscripted or general guidelines and suggestions for adapting</td>
</tr>
</tbody>
</table>
## Two Approaches to a Medication Adherence Trial: EFFICACY Trial vs. PRACTICAL Trial (Glasgow & Steiner)

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<th>Design Decision</th>
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<th>Pragmatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>How to monitor implementation of advice protocol?</td>
<td>Careful assessment of fidelity to protocol, and intensified intervention if not optimal</td>
<td>Qualitative assessment of advice actually delivered by pharmacists</td>
</tr>
<tr>
<td>How to monitor adherence?</td>
<td>Active, continuous assessment with electronic medication monitors</td>
<td>Surveillance by patient self-report and/or prescription refill records</td>
</tr>
<tr>
<td>How to monitor impact on cholesterol?</td>
<td>Fasting cholesterol levels drawn at pre-specified intervals during additional visits for that purpose</td>
<td>Fasting cholesterol levels drawn in the course of routine practice visits</td>
</tr>
<tr>
<td>Which patient subgroups to monitor for differences in effectiveness?</td>
<td>Few subgroups assessed (due to exclusions in recruitment), homogeneous patients not on other medications</td>
<td>Multiple pre-specified subgroups (particularly for subgroups oft excluded in an efficacy trial, e.g. individuals with multi-morbidity, limited cell phone comfort, low health literacy/numeracy participants)</td>
</tr>
<tr>
<td>Duration of follow-up?</td>
<td>Short-term (e.g. 3-6 months), allowing identification of individuals who soon stop treatment</td>
<td>Long-term (12-24 months), allowing identification of individuals who later restart treatment</td>
</tr>
<tr>
<td>Continuation of intervention?</td>
<td>To end of grant funding</td>
<td>Long-term incorporation into clinic operations</td>
</tr>
<tr>
<td>Does this intervention have any effects, positive or negative, on clinic operations? Cost of intervention</td>
<td>Not relevant to assess Not assessed</td>
<td>Critical to assess through staff interviews, observations and qualitative assessments Assessed from perspective of adopting organization and patient, includes cost-effectiveness indices</td>
</tr>
</tbody>
</table>
Be Fit, Be Well

A randomized weight reduction and maintenance effectiveness trial in routine clinical practice in Boston Community Health Centers
The focus of the study:

- Help obese, low-income adults lose weight, become more active, and keep their blood pressure under better control
- Aim was to set realistic and meaningful goals that lead to small, sustainable behavior change that will continue past the end of the study

Intervention Components

• Goal-Setting & Attainment, Using Various Tools and Types of Support
  ▪ Electronic Support
    • Web or IVR Phone System
  ▪ Socio-environmental support
    • Community Health Worker
    • Individual Coaching
    • Group Activity Sessions
Avoid High-calorie Snacks

Be Fit, Be Well recommends that you stay away from high-calorie snacks.

Sweets like cookies and candy have lots of calories, but not much nutrition. Salty foods like chips have way too much fat and salt. Eat healthy snacks instead.

Get Brisk Exercise

Be Fit, Be Well recommends that you do 20 minutes of brisk exercise every day.

You should do this all at once, without stopping. Start slow and aim for this goal. Work toward exercising hard enough to make you sweat.
Health Information Comparison Condition

• Comparison Condition participants receive:
  ▪ General health information about blood pressure, diet and activity
  ▪ Clinic visit every 6 months where Weight/BP measurements are taken
  ▪ Grocery cards: $50 x 4 and $75 at completion of study (total $275 over 2 years)
  ▪ Encouragement to continue with their doctor’s instructions for care.
  ▪ NHLBI Weight Loss Pamphlet
Comparison Conditions in Pragmatic Trials

• Must be a Realistic Alternative

• Not Placebo or Wait List or No Treatment

• Can Be Component or Less Expensive Intervention

• Consider “Minimal Intervention Needed for Change (MINC)”

• What is “Usual Care”?
Questions/Comments?
The Problem with Labels

• Labels such as pragmatic or explanatory are an over simplification and imply a dichotomy.

• In reality, there is a continuum between the extreme cases of either type, and very few actual studies are completely explanatory or totally pragmatic.
The Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)

Describes ten domains that affect the degree to which a trial is pragmatic or explanatory.

1. Participant eligibility criteria
2. Experimental intervention flexibility
3. Practitioner expertise (experimental)
4. Comparison intervention
5. Practitioner expertise (comparison) outcome
6. Follow-up intensity
7. Primary trial outcome
8. Participant compliance
9. Practitioner adherence
10. Analysis of primary

**A**

**PRAGMATIC STUDY**

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

**B**

**EXPLANATORY STUDY**

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

- *PRECIS* CAN BE applied by:
  - a design team during the planning stages
  - by an implementation team
  - post-hoc by reviews from study report

- The graphical representations are helpful for readily identifying domains that are not as pragmatic or explanatory as the trial designers desired.
Summary and Issues for Discussion

Strengths of PRECIS

- Enhances transparency
- Will greatly improve information reported for reviews
- Gets around “either/or” debates
- CONSORT endorsement will enhance wide adoption
RE-AIM **Evaluability Questions for eHealth**

- What percent and what types of patients are likely to **Receive** this program;
- For whom among them is the intervention **Effective**; in improving what outcomes; what broader effects and potential negative consequences?
- What percent and what types of settings and practitioners are likely to **Adopt** this program;
- How consistently are different parts of the program likely to be **Implemented** across settings, clinicians, and patient subgroups, ....... and at what cost;
- And how well is the eHealth program and its effects likely to be **Maintained**?

Pragmatic Trials: Take Home Points

• Real-world focus—relevant to stakeholders

• Multi-level representativeness and diversity

• Endorsed by CONSORT; PRECIS criteria

• Congruent with Comparative Effectiveness, PCORI, VA, HMO, PBRN, and HCS COLLABORATORY research

Bottom Line: **TRANSPARENCY AND RELEVANCE**
References


QUESTIONS ANSWERED HERE EVEN THE SILLY ONES
What is the Outcome?
When Too Much Focus Can Hide Harm

Robert M. Kaplan
Director, Office of Behavioral And Social Science Research
National Institutes of Health, Office of the Director
Reductionism and Linear Thinking: Are People Like Cars?

• Sir Isaac Newton -- discrete components assumed to operate independently from one another.

• Ackoff - industrial revolution (18th Century England) initiated ways of thinking that dominated nearly all fields of science for several centuries. Core concepts:
  • reductionism,
  • analysis,
  • mechanism
Brunswick’s “Molar vs Molecular Reductionism: The Outcome Researcher Perspective

Disease: Shortens life or interferes with life quality now or in the future

We Look at Outcomes Differently

- There are only two outcomes of importance
  - Length of life
  - Quality of life
    - Patient reported outcomes
    - Functioning
    - Symptoms/problem

- Physiological measures are only important if they relate to length or quality of life
- Overall outcome represented as QALY
What is the problem?

Focus on the specific...
- Blood pressure
- Cholesterol
- Deaths from breast cancer.....

Can Mask the big picture
- Deaths from all causes
- Quality of Life
- Quality-adjusted life years
Total mortality in the Aspirin component of the Physician’s Health Study. Overall the number of physicians who died was identical in the Aspirin and the Placebo conditions (From Kaplan, NEJM 1989)
Cancer mortality in the Health Insurance Plan of New York

- 60,000 women assigned to mammography or usual care
- After 10 years 147 deaths in the mammography group and 192 deaths in usual care group
- 23% reduction in cancer deaths
Cancer mortality in the Health Insurance Plan of New York

- Lower portion shows cancer deaths, upper shows non-cancer deaths
- No difference in survival between screened and unscreened women
Median Glycated Hemoglobin Levels at Each Study Visit ACCORD Trial (NEJM, 358)
Kaplan-Meier Curves for the Primary Outcome and Death from Any Cause

A Primary Outcome

B Death from Any Cause

No. at Risk
Intensive therapy 5128 4972 4803 4803 3250 1748 523 506
Standard therapy 5123 4971 4700 3180 1642 499 480

Patients with Events (%)
VADT Outcomes
(from NEJM 360;2
January 8, 2009)

Despite reductions in HbA1c, no noticeable benefit for any outcome. But, there was evidence of harm

Table 2. Hypoglycemic Episodes.†

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Therapy (N = 899)</th>
<th>Intensive Therapy (N = 892)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./100 patient-yr</td>
<td></td>
</tr>
<tr>
<td>Episodes with impaired consciousness</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Episodes with complete loss of consciousness</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Nocturnal episodes</td>
<td>44</td>
<td>152</td>
</tr>
<tr>
<td>Total episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With symptoms</td>
<td>383</td>
<td>1333</td>
</tr>
<tr>
<td>Without symptoms</td>
<td>49</td>
<td>233</td>
</tr>
<tr>
<td>Relieved by food or sugar intake</td>
<td>421</td>
<td>1516</td>
</tr>
<tr>
<td>Measurement of blood glucose during episode</td>
<td>348</td>
<td>1392</td>
</tr>
<tr>
<td>With documented blood glucose &lt;50 mg/dl</td>
<td>52</td>
<td>203</td>
</tr>
</tbody>
</table>

* P<0.001 for all differences between the two groups.
Mean Systolic Blood-Pressure Levels at Each Study Visit

![Graph showing systolic pressure levels over time for Standard and Intensive groups, with mean number of medications prescribed and number of patients for each group]

Adverse Events in Hypertension Component of ACCORD

- Hypotension
- Syncope
- Hyperkalemia
- Bradycardia

Graph showing the comparison between Intensive and Standard treatments for the mentioned adverse events.
603 patients with an estimated glomerular filtration rate (GFR) of 15.0 to 35.0 ml per minute per 1.73 m2 of body-surface area and mild-to-moderate anemia (hemoglobin level, 11.0 to 12.5 g per deciliter) randomly assigned to

- a target hemoglobin value in the normal range (13.0 to 15.0 g per deciliter, group 1) or the
- subnormal range (10.5 to 11.5 g per deciliter, group 2). per deciliter --triggered treatment at 10.5 g (group 2).
Aggressive treatment effectively increases hemoglobin, but....

CREATE Median Hemoglobin Levels in the Intention-to-Treat Population during the Study.
Percent of Patients Requiring Dialysis in CREATE Study by Group
Percent Adverse Reactions (selected) by Group in CREATE
Outcomes in CHIOR Trial

**Primary Composite End Point**

- **High-hemoglobin group**
- **Low-hemoglobin group**

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>High-hemoglobin</th>
<th>Low-hemoglobin</th>
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<tbody>
<tr>
<td></td>
<td>715</td>
<td>717</td>
</tr>
<tr>
<td></td>
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<td>660</td>
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</table>
• Dronedarone restores sinus rhythm and reduces hospitalization or death in intermittent atrial fibrillation.

• It also lowers heart rate and blood pressure and has antiadrenergic and potential ventricular anti-arrhythmic effects.

• Dronedarone **increased** rates of heart failure, stroke, and death from cardiovascular causes in patients with permanent atrial fibrillation who were at risk for major vascular events.
In RCT patients with idiopathic pulmonary fibrosis randomly assigned to one of three groups
- combination of prednisone, azathioprine, and NAC (combination therapy),
- NAC alone, or
- placebo.

The primary outcome was the change in longitudinal measurements of forced vital capacity during a 60-week treatment period.
There Are Many Examples From the Clinical Trial Literature

- Cardiac Arrhythmia Suppression Trial (CAST)
- The Physicians Health Study (PHS)
- Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)
- Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)
- COURAGE
- Woman’s Health Initiative WHI
- Action to Control Cardiovascular Risk in Diabetes (ACCORD)
- Canadian National Breast Screening Study (CNBS)
- Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women
- .....
My point is…

- In trial after trial the intermediate endpoint confirmed the value of treatment.
- Simple modeling outcomes using intermediate endpoints would have shown great benefit for treatment.
- But, in each case, the modelers would have been wrong.
Conclusions

- Interventions are often guided by very simple mental models of disease
  - These models often assume relationships are linear
  - Disease is often non-linear
- Outcomes researchers focus on different aspects of the data
  - Total mortality
  - Quality of Life
- Aggressive care is not always the best care
- There is still a place for large RCTs
- Better modeling, using more complex models may be offer important insights