The Pragmatic Clinical Trial in a Learning Healthcare System

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The Birth of the Pragmatic Clinical Trial (PCT) Concept

1967


“Pragmatic” – aimed at decision making
“Explanatory” - elucidation of causality
Archie Cochrane’s 3 Questions

- “Can it work”?
- “Will it work”?
- “Is it worth it”? ¹

“The [conventional, explanatory] clinical trial is the best way to assess whether an intervention works, but it is arguably the worst way to assess who will benefit from it.” ²

Explanatory Clinical Trial

Seeks to answer Archie Cochrane’s first question

“Can an intervention work under ideal conditions?”
Explanatory Clinical Trial

- Designed to assess the efficacy
- Selected patients, multiple exclusions
- Rarely compare treatments head-to-head
- Selected settings
- Strict protocol adherence
- Limited outcomes
- Short follow-up
Pragmatic Clinical Trials

Seeks to answer Archie Cochrane’s second question

“Will the intervention work under usual care conditions?”
Pragmatic Clinical Trials

- Designed to assess effectiveness
- Broad patient inclusion criteria
- Relevant alternative treatments
- Routine clinical care settings
- Flexible protocol
- Clinical, functional, economic outcomes
- Adequate follow-up
Introducing…

PRECIS

The Pragmatic-Explanatory Continuum Indicator Summary*


Why Does the Pragmatic vs. Explanatory Distinction Matter?

<table>
<thead>
<tr>
<th></th>
<th>Negative Results</th>
<th>Positive Results</th>
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<tbody>
<tr>
<td>Explanatory</td>
<td>Unlikely to work in routine practice</td>
<td>May or may not work in routine practice</td>
</tr>
<tr>
<td>Pragmatic</td>
<td>Intervention may still work under ideal conditions</td>
<td>Likely to be successful in routine practice</td>
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Example: Anti-Depressant PCT and Clinical Policy Implications


Two perspectives:
- Managed Care (payer/provider)
- Manufacturer
Health Plan Perspective

Fluoxetine (Prozac, first SSRI) vs generic tricyclics

- RCT results: ~ efficacy, fewer SE
- Price ~ 10-20 times higher!

Fluoxetine 1st line: Overwhelm entire psych budget

Pending P&T decision: Limit fluoxetine to 2nd line
Manufacturer Perspective

Noted increased restrictive US formularies

Concerned that limiting fluoxetine to 2nd line:
- Not good for patients
- Not good for sales (duh!)

Belief: Fluoxetine as 1st line would lead to:
- Good value for $ for managed care/health plans
- Better patient care

Willing to sponsor a fair test: a true pragmatic trial
Solution: Partner to Sponsor PCT

Research Question: Does initial selection of fluoxetine result in better clinical, quality of life, and economic outcomes compared with initial selection of less expensive TCAs?

NOTE: The research question concerned the clinical decision policy not the (comparative) efficacy of the drugs.
Study Design Issues

- Recruitment: Routine primary care encounter
- Randomization to imipramine, desipramine or fluoxetine
- Naturalistic, open label: Physician control over dosage and duration of therapy
- No other clinical protocol requirements (e.g. cross-overs, under-dosing, discontinuation allowed...but were monitored)
Outcome Measure

- Measures of depression severity recorded after randomization to establish baseline
  - Note: patients did not need to meet major depression criteria to be included (to be true to community practice)

- HRQL recorded via periodic phone calls

- Medical utilization and costs from claims data base

- 536 patients followed for 6 months (91% complete) and 2 years (72% complete)
Study Findings (ITT)

- Discontinuation rates: Fluoxetine lower vs. TCAs
- Side effects: Fluoxetine lower vs. TCAs
- HRQL outcomes: No differences
- Medical costs: No differences
Clinical Policy Implications

- SSRIs re-instituted as 1st-line therapy

- Patient and physician preferences became basis for treatment selection

- MC efforts focused on improving:
  - Detection of depression by primary care physicians
  - Treatment of depression by primary care physicians
  - Adherence to antidepressant therapy
Definition of PCT

“…a prospective comparison of a community-, clinical-, or system-level intervention and a relevant comparator in participants who are similar to those affected by the condition(s) under study and in settings that are similar to those in which the condition is typically treated.”

Thank You