Making pragmatic trials work

Identifying and overcoming challenges to generate ‘real-world’ relative effectiveness estimates

Iris Goetz, work package 3
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Overview

1. Why pragmatic trials?
2. What are pragmatic trials?
3. Practical challenges and impact
4. A decision support tool for trial designers: PragMagic
Why pragmatic trials?

- Relative effectiveness data needed to guide decision makers

- Pragmatic trials combine
  - the strength of “traditional” RCTs: randomization addresses baseline comparability
  - the usual care set up of observational studies: results generalizable to target population

BUT:

design crucial for validity, generalizability & feasibility
GetReal work package 3

**aim**
- facilitate the design & conduct of pragmatic trials

**by**
- insights: consequences of design & operational challenges
- visualize complex interplay systematically: decision support tool

**to**
- maximize generalizability of trial findings
- ensure validity & operational feasibility
### What are pragmatic trials?

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<tr>
<th>can tx work? ➔ EFFICACY</th>
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<tbody>
<tr>
<td>Hypothesis testing</td>
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<td>ideal circumstances</td>
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<th>Assess cause–effect of drug</th>
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<td>Rigid protocol</td>
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<td>Selective inclusion</td>
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<th>minimize variation:</th>
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<td>Data collection &gt; usual care</td>
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<td>outcomes research relevant</td>
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**WHAT?**
- Important to decision/policy makers & patients
- Generalizable
- Real-world alternatives

**WHY?**
- Inform decision makers
- Real-world alternatives

**HOW?**
- Protocol reflecting usual care
- Protocol reflecting usual care

**WHO?**
- Broad inclusion
- Selective inclusion

**METHOD?**
- Data collection = usual care
- Data collection > usual care

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The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution. 

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Challenges in designing and conducting pRCTs

Operational challenges:

different & unanticipated

Influence of design choices:

validity
generalizability
precision
feasibility
acceptability

Complex interplay:

design choices, operational challenges & implications

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Key elements of trial design

- Intervention comparator
- Outcomes selection
- Data collection
- Safety
- Quality assurance
- Statistical issues

- Patient / Participant
- Site / prescriber
- Regulatory, Ethical

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Example: site selection

Which sites to select?

- 1°, 2°, 3° sites? In/out patients?
- N° of sites?
- Logistics?
- IT requirements?

Location:
- multiple countries/regions?
- Ethical, legal, language differences?
- Differences in SOC/Usual Care?

Site research
- additional resources necessary?
- Willingness to participate?
- Extra training?

Representative site recruitment
- Use existing relationships? networks?
- Eligibility screen?
- Random Site selection? Other?
- Specific recruitment technique?
- N° of sites?
- Logistics?
- IT requirements?
- Use existing relationships? networks?
- Eligibility screen?
- Random Site selection? Other?
- Specific recruitment technique?
Impact on generalizability, validity, precision

❖ Generalizability:
  • Are the sites generalizable to RWE target population?
  • Is the usual care practiced in the sites generalizable?
  • Are the comparators used generalizable?

❖ Risk of Bias:
  • Are there strong treatment preferences in open label trials?
  • Differential loss to follow up?

❖ Precision:
  • Are measurements in usual care inconsistent/variable/missing?

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Summary

- Specific design choices can have impact on validity, generalizability, precision and feasibility
- Various stakeholders should be involved in design process to realize most pragmatic approach suitable to answer the research question.
- When carefully executed, pragmatic trials have the potential to deliver valid RWE earlier in development/evaluation
- WP3 of GetReal will provide decision support tool for pragmatic trials: PragMagic
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<th>Title</th>
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<td>1 Pragmatic trials and real world evidence (intro paper)</td>
<td>Revisions</td>
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<td>2 Selection and inclusion of usual care sites</td>
<td>Revisions</td>
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<td>3 Selection, recruitment and retention of participants</td>
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<td>5 Defining questions, choosing comparators, allocating treatments</td>
<td>Under GetReal review</td>
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<td>6 Outcome selection and definition</td>
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<td>7 Monitoring patient safety and trial conduct</td>
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<td>8 Data collection and management</td>
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