Pragmatic Trials – An overview

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Background

- Features & goals of “traditional” clinical trials:
  - Very controlled protocol: Population (inex), environment, ...
  - Demonstrate efficacy and safety of a new treatment
  - Designed to show that treatment “works”

  ⇒ High internal validity

- What about external validity?
  - Often important to establish clinical effectiveness
  - Generalizability of results? Setting too artificial?

  ⇒ Demonstrate treatment effect in heterogeneous setting, assumed to reflect the “real world” with regard to population, environment, ...
Background

Ideas to run trials in a “real-world” setting:

- Data sources (health records, registries, social media, ...)
- Collection of data (home monitoring, e-devices, apps, ...)
- Design of trials (prospective/retrospective, randomized or not, ...)

⇒ Increase external validity (!?)

“Real-world” trials and randomization – a contradiction?

“Real world evidence and randomisation are two fully compatible concepts”

← Sherman et al. (2016) [1]

“Statisticians can also perform a valuable service by continually reminding people about what a powerful tool randomization is.”

← Robert M Califf (2016) [2]
Pragmatic Trials

• Pragmatic **randomised** trials (PrCTs) are a way to estimate a treatment's effectiveness

• First paper to discuss pragmatic approaches in clinical trials goes back to the 1960s (Schwartz and Lellouch (1967) [3])

“[…there is a continuum between pragmatic and explanatory trials [...].”


“Very few trials can be fully pragmatic.”

-- Ford and Norrie (2016) [5]

Note: By *explanatory trials* the “classical” confirmatory randomized trials are meant
Pragmatic Trials - Definition

- Real world population
- Heterogeneous population
- Minimal/no inclusion/exclusion criteria
- Intention to inform decision making (FDA, Califf 2016 [2])
- Potential for cluster-randomization
- Randomized but often open label
- Complex interventions
- Only few but meaningful endpoints
- Broad range of outcomes (FDA, Califf 2016 [2])
- Every step of a CT can be relaxed to make it pragmatic (EMA, workshop PAES studies)
- Follow up akin to observational study (EMA, workshop PAES studies)

Pragmatic Randomized Clinical Trial

- Patients similar to patients who would receive treatment if it became usual care (population usually unknown)
- Real life setting
- Routine clinical practice
- Staff with typical experience
- Bringing the trial to patients
- “Learning health care systems”
- EHR
- Social media
- Personal device (smartphone)

- Realistic sample size
- Intention to inform decision making (FDA, Califf 2016 [2])
- Potential for cluster-randomization
- Randomized but often open label
- Complex interventions
- Only few but meaningful endpoints
- Broad range of outcomes (FDA, Califf 2016 [2])
- Every step of a CT can be relaxed to make it pragmatic (EMA, workshop PAES studies)
- Follow up akin to observational study (EMA, workshop PAES studies)
Not a single, generally accepted definition (yet) ⇒ some (common and overlapping) ideas of a definition in:


A definition from IMI GetReal [7]:

“A study comparing several health interventions among a randomised, diverse population representing clinical practice, and measuring a broad range of health outcomes.”
Pragmatic Trials - Definition

Pragmatic Clinical Trials (PrCT) are randomized clinical trials that
- enroll a **real-world population**, i.e., a population close to the patient population that would receive the treatment in practice
- are conducted in a **real-world setting** (e.g., rather GPs, community sites than professional study sites)
- capture the **relevant outcomes** to inform optimal healthcare treatment decisions
- include an **appropriate comparison arm** depending on the question of interest
Pragmatic Trials - CT.gov Search Results for PrCT

Conducted in Sep 2017

<table>
<thead>
<tr>
<th>Search terms</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>pragmatic AND randomized</td>
<td>450</td>
</tr>
<tr>
<td>pragmatic AND randomised</td>
<td>94</td>
</tr>
<tr>
<td>real world AND randomized</td>
<td>271</td>
</tr>
<tr>
<td>real world AND randomised</td>
<td>15</td>
</tr>
<tr>
<td>total</td>
<td>830</td>
</tr>
</tbody>
</table>

Based on search criteria (unique entries) n=732

Exclude studies not listed as Interventional n=40

Unique entries of interventional studies n=692

Exclude studies not listed as randomized n=29

Unique entries of randomized studies n=663

Exclude studies not funded by Industry n=580

Unique entries of studies funded by Industry n=83

Pragmatic Trials - CT.gov Search Results for PrCT

- Review of industry funded studies titles ⇒ 20 titles allow for identification as clearly PrCT (or included ‘effectiveness’ or ‘real world’)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Results (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II/III</td>
<td>1</td>
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<tr>
<td>III</td>
<td>2</td>
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<tr>
<td>IV</td>
<td>11</td>
</tr>
<tr>
<td>not listed</td>
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</table>

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Results (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>2</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory</td>
<td>5</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>3</td>
</tr>
<tr>
<td>Oncology</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
</tbody>
</table>

- Limitation: Very few trials identified as pragmatic
  Not all pragmatic trials are easily identifiable through a database search if relevant terms like ‘pragmatic’ or ‘real world’ were not used e.g. in the title

## Pragmatic Trials - EudraCT Search Results for PrCT

<table>
<thead>
<tr>
<th>Search terms</th>
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</tr>
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<tbody>
<tr>
<td>pragmatic AND randomized</td>
<td>15</td>
</tr>
<tr>
<td>pragmatic AND randomised</td>
<td>21</td>
</tr>
<tr>
<td>real world AND randomized</td>
<td>6</td>
</tr>
<tr>
<td>real world AND randomised</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total in EudraCT</strong></td>
<td>47</td>
</tr>
<tr>
<td><strong>PrCT after title review</strong></td>
<td>26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>CNS</td>
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<td>2</td>
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<td>Cardiovascular</td>
<td>1</td>
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<tr>
<td>Oncology</td>
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<tr>
<td>Other</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>26</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of sponsor</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical company</td>
<td>8</td>
</tr>
<tr>
<td>University / University hospital</td>
<td>13</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>26</td>
</tr>
</tbody>
</table>

- 18 out 26 trials conducted in Great Britain
- Only 3 trials marked as completed
- **Same limitations** of search as with CT.gov
Pragmatic Trials – Assessing degree of pragmatism

- [https://www.pragmagic.eu](https://www.pragmagic.eu)

<table>
<thead>
<tr>
<th>Domains of PRECIS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility: Who is selected to participate in the trial?</td>
</tr>
<tr>
<td>Recruitment: How are participants recruited into the trial?</td>
</tr>
<tr>
<td>Setting: Where is the trial being done?</td>
</tr>
<tr>
<td>Organisation: What expertise and resources are needed to deliver the intervention?</td>
</tr>
<tr>
<td>Flexibility: adherence: What measures are in place to make sure participants adhere to the intervention?</td>
</tr>
<tr>
<td>Flexibility: delivery: How should the intervention be delivered?</td>
</tr>
<tr>
<td>Primary analysis: To what extent are all data included?</td>
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<tr>
<td>Primary outcome: How relevant is it to participants?</td>
</tr>
<tr>
<td>Follow-up: How closely are participants followed-up?</td>
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Examples - Salford Lung Study & AIRWISE

GSK, 2 trials: one for COPD, and one for asthma, pragmatic randomised open label Phase III trials) [9, 10]

- “World’s first pragmatic randomized controlled trial of an investigational medication” [9]
- Fluticasone furoate/vilaterol vs. existing COPD/existing asthma maintenance therapy
- Study conducted around Salford, high COPD prevalence, single hospital, established electronic medical record, GPs and pharmacies collaborated
- Minimal exclusion criteria
- Primary outcome:
  - for COPD: mean annual rate of COPD exacerbations
  - for asthma: asthma control test at week 24

- “[...] phase 4 clinical trial aiming to assess how commonly prescribed medicines may decrease the worsening of symptoms in [...] COPD [...]” (www.copdnews.com, OCT 6, 2017)
- “The AIRWISE trial (NCT03265145) is described as the world’s largest ever pragmatic clinical trial, meaning it is designed to test a medication’s effectiveness in routine clinical practice settings.” (www.copdnews.com, OCT 6, 2017)
- 3200 participants randomized parallel assessment
- Started September 2017, estimated completion in June 2020
- Primary outcome: Time to first moderate or severe COPD exacerbation over 12 months
WHO sponsored, vaccine from Merck Sharp & Dohme, ring vaccination cluster randomized open-label clinical trial in Guinea/Sierra Leone during Ebola outbreak in 2015 [11]

- Vaccine for Zaire Ebola Virus
- **Ring/cluster** i.e. all contacts and contacts of contacts of confirmed Ebola case
- 1:1 rand. to immediate or delayed vaccination, i.e. 21 days later, of all people in the cluster
- Immediate vaccination: 51 cluster with n=4539 contacts and contacts of & delayed vaccination: 47 clusters with n=4557 contacts and contacts of contacts identified
- Primary outcome: laboratory confirmed case of Ebola virus disease with onset 10 days or more until 31 days from randomisation
“[...] access to statistical support and collaboration is among the most critical needs identified by clinical and translational investigators [...]”

“[...] it is imperative that we work to expand the pipeline of well-trained statisticians [...]”

-- Robert M Califf (2016) [2]
References


[8] Loudon K, et al., The PRECIS-2 tool: designing trials that are fit for purpose; BMJ 2015; 350:h2147
