Pragmatic clinical trial design: experience, advice, and key decision points to consider

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Disclosures

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Learning Objectives

1) Summarize key study decisions and considerations when designing pragmatic clinical trials

2) Identify potential study design types

3) Determine the rationale and pros/cons for study design selection in existing ED-based pragmatic clinical trials
Agenda

• Pragmatic-Explanatory Continuum
  – PRECIS-2 tool

• Additional Study Decisions
  – Randomization
  – Human subjects concerns

• Study Design Types

• Example Pragmatic Components from ED Studies
  – PollEverywhere
Pragmatic – Explanatory Continuum

• Explanatory: Can this intervention work under ideal conditions?

• Pragmatic: Does this intervention work under usual ‘real-world’ conditions?
• **PRagmatic Exploratory Continuum Indicator Summary tool**
  – Developed to help investigators work through study design decisions to avoid designing a trial that did not meet their own intentions

• 2015 – PRECIS-2 Wheel Diagram
  – Eligibility, recruitment, setting, organization, flexibility – delivery, flexibility – adherence, follow-up, primary outcome, and primary analysis
ELIGIBILITY - Who is selected to participate in the trial?

RECRUITMENT - How are participants recruited into the trial?

SETTING - Where is the trial being done?

ORGANISATION - What expertise and resources are needed to deliver the intervention?

FLEXIBILITY: DELIVERY - How should the intervention be delivered?

FLEXIBILITY: ADHERENCE - What measures are in place to make sure participants adhere to the intervention?

FOLLOW-UP - How closely are participants followed-up?

PRIMARY OUTCOME - How relevant is it to participants?

PRIMARY ANALYSIS - To what extent are all data included?
• Eligibility criteria
  – Limited exclusion criteria

• Recruitment
  – Minimal overt recruitment effort

• Setting
  – Consider high and low resource EDs

• Organization
  – Minimal reliance on increased staff number or training requirements
• Flexibility (delivery)
  – No rigid prescription for intervention implementation

• Flexibility (adherence)
  – Allowance of end user to modify the intervention with certain constraints
• Follow-up
  – No more follow-up than usual care and no reliance on additional data collection

• Primary outcome
  – Easily measured and salient to stakeholders

• Primary analysis
  – Intention-to-treat analysis
Additional Study Decisions

• Randomization
  – Is the phenomenon of interest something that takes place primarily at the level of the individual participant? Or group?
  – If randomized at individual level, can clinicians avoid contamination?
  – Correlation of participant outcomes within a cluster?
    • Intraclass correlation coefficient (ICC)
Additional Study Decisions

• Human Subjects Concerns
  – Single, centralized IRB to eliminate redundant reviews across multiple sites
  – Default regulatory board recommendation for written informed consent?
    • Often incompatible with PCT study’s nature and intent
  – Additional consent options:
    • Broadcast notification
    • Opt-out consent
    • ‘Short form’ consent
    • Electronic consent
Additional Study Decisions

• Human Subjects Concerns (cont’d)
  – Four criteria of the Common Rule must be met to obtain a waiver of informed consent
    • “...research could not practically be carried out without the waiver or alteration”
  – Language to consider with regulatory board:
    • Counter to the goal of PCTs, non-routine workflow procedures associated with informed consent process can hinder recruitment, introduce selection bias, and impact generalizability.
Choosing the Right Pragmatic Trial Study Design
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Pros/Cons/Rationale</th>
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</table>
| Parallel      | Pro – No inadvertent contamination by unplanned interventions or cross-over  
Con – Often require larger sample sizes due to within- and between-subject variation, which may increase cost and resource utilization  
Rationale – Most common study type, appropriate if concerns regarding cross-over may be present or if the disease or condition being studies may progress over time.                                                                                                   |
| Cross-over    | Pro – Comparison of treatment effect *within* participant  
Con – Risk of contamination if the intervention cannot be turned ‘on’ and ‘off’ without residual practices being carried over from one period to the next; Duration of follow-up generally longer  
Rationale – Appropriate if concerns exist regarding temporal confounders or significant population variation that may prevent balanced distribution between groups.                                                                                       |
# Study Design Types

## Parallel

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## Crossover

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The table uses color coding to represent different phases:
- **Intervention** (Dark Blue)
- **Control** (Light Green)
- **Wash-out Period** (Light Blue)
- **Intervention Component** (Green)

*SAEM22*
## Study Design Types

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<tr>
<th>Study Type</th>
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| Factorial           | Pro – Efficient, in that multiple research questions may be answered with limited sample sizes  
                       Con – Complex in design and statistical analysis; Difficulty meeting inclusion criteria for both intervention(s) or components  
                       Rationale – Allows assessment of several intervention(s)/components and even interactions between them, often providing information whether varying levels or doses of an intervention affects different populations in different ways. |
| Stepped wedge       | Pro – All participants receive the intervention; Possible to control for external temporal trends  
                       Con – Increased complexity may require additional statistical expertise and resources; May be subject to temporal confounding  
                       Rationale – Developed to address feasibility and ethical concerns that all participants should eventually receive the intervention within the study timeframe when the intervention is anticipated to produce a positive outcome. |
### Study Design Types

#### Time

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*Colors represent: Intervention, Control, Wash-out Period, Intervention Component*
Example Pragmatic Study Components
Example #1

- Effectiveness of initial LTI insertion vs ETI in OHCA
- EMS agencies from the ROC
- Multicenter pragmatic cluster-crossover trial
- Initial LTI associated with increased 72-hr survival compared to ETI insertion
Methods

• The trial included adults (age ≥18 years or per local interpretation) with nontraumatic OHCA treated by participating EMS agencies and requiring anticipated ventilatory support or advanced airway management
This section of the Methods is a pragmatic example of which PRECIS-2 domain?

Setting
Eligibility
Recruitment
Organization
Additional pragmatic components

- Leveraged existing research infrastructure of Resuscitation Outcomes Consortium
- Included “all” adult OHCA requiring airway management
  - Few exclusions
- EMS agencies used their own:
  - Airway equipment
  - Clinical protocols
  - Training practices
- Limited data collection
  - Only variables normally collected by ROC OHCA Registry
Example #2

- Effectiveness of a discharge follow-up phone call
- Single-center pragmatic RCT
- Outcome: 30-day hospital readmissions
Methods

• ...into the operations of daily inpatient care without disturbing the workflow of medical providers.
• We requested a waiver of consent from our IRB given several considerations...The trial examines the effectiveness of a newly established but existing clinical programme calling patients within 7 days of hospital discharge to support successful transition to outpatient care. As a result the intervention is in active use, but its impact is unclear, thus demonstrating equipoise.
• We identify eligible patients via a custom programmed discharged patient report generated from the medical centre’s electronic health record admission, discharge and transfer (ADT) system each weekday morning. This auto-generated report...
This section of the Methods is a pragmatic example of which PRECIS-2 domain?

- Recruitment
- Primary Outcome
- Organization
- Setting
Example #3

- Describe use of new decision support tool and order set for inpatient physicians

- Physicians randomized to the intervention helped physicians place more orders for tobacco treatment medication, referrals to state smokers’ quitline, and emails to PCPs.
Methods

• Of note, the alert has three functions that were pre-checked, for the physician, if s/he accepted the alert: (1) a referral to the Connecticut State Smokers’ Quitline, (2) opening of the E-STOPS order set, and (3) adding “tobacco use disorder” to the patient’s problem list. This saved clinician time while allowing them the autonomy to not order the interventions if they chose.
This section of the Methods is a pragmatic example of which PRECIS-2 domain?

- Flexibility (delivery)
- Setting
- Recruitment
- Follow-up
Example #4

- Compare a decision aid with usual care to identify children at high risk of ciTBI
- Decision aid increased parent knowledge, decreased decisional conflict, and increased involvement in decision-making.
- The intervention did not significantly reduce the ED CT rate, but did decrease healthcare utilization within 7 days.
Methods

• We analyzed all parent-child dyads in the arm to which they were randomized consistent with the principle of intention-to-treat.
This section of the Methods is a pragmatic example of which PRECIS-2 domain?

- Primary Outcome
- Primary Analysis
- Recruitment
- Flexibility (adherence)
Compare two models of palliative care

- Nurse-led telephonic case management
- Specialty outpatient

Differences identified in QoL, symptom burden, and loneliness
Methods

• This RCT began recruitment in April 2018 and is currently enrolling at 18 emergency department (ED) sites across the United States (US), with locations representing the geographic diversity of the country.
This section of the Methods is a pragmatic example of which PRECIS-2 domain?

- Eligibility
- Recruitment
- Organization
- Setting
# PRECIS-2

## Table 1. PRECIS-2 score for PRIM-ER Domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Score*</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility Criteria</td>
<td>5</td>
<td>Broad eligibility criteria include all older adults 66+ who present to one of the participating EDs with high short-term mortality; very few exclusions (hospice in prior 12 months)</td>
</tr>
<tr>
<td>Recruitment Path</td>
<td>5</td>
<td>No individual patient participant consent or recruitment</td>
</tr>
<tr>
<td>Setting</td>
<td>5</td>
<td>EDs treat all patients regardless of insurance status or ability to pay</td>
</tr>
<tr>
<td>Organization intervention</td>
<td>5</td>
<td>Intervention will be delivered by current emergency provider workforce</td>
</tr>
<tr>
<td>Flex of experimental intervention—Delivery</td>
<td>4</td>
<td>Core content (nursing and emergency medicine palliative care content, communications training) is standardized yet the delivery can be tailored to each ED based on their current workforce (e.g., physician assistant or post-graduate trainee involvement) and local EHR</td>
</tr>
<tr>
<td>Flex of experimental intervention—Adherence</td>
<td>4</td>
<td>All emergency providers will be invited to participate with varying levels of contact hours depending on their role; monetary incentives ($50-100) and continuing education credits will be provided to encourage adherence</td>
</tr>
<tr>
<td>Follow up</td>
<td>5</td>
<td>No additional patient follow up as part of trial</td>
</tr>
<tr>
<td>Outcome</td>
<td>4</td>
<td>Acute care admission versus discharge home, healthcare utilization in the 6 months following the index ED visit, and survival are all highly relevant to patient participants</td>
</tr>
<tr>
<td>Analysis</td>
<td>5</td>
<td>Intention to treat analysis regardless of compliance with per protocol sensitivity analysis</td>
</tr>
</tbody>
</table>

*1=very explanatory, 2= rather explanatory, 3=equally pragmatic/explanatory, 4=rather pragmatic, 5=very pragmatic
Example #6

• Integrate and disseminate Clinical Decision Support to promote ED-initiation of buprenorphine/naloxone

• Parallel group randomized pragmatic trial in 20 EDs
Methods

• With the exception of some physician-level outcomes (e.g., the proportion of attendings with DATA 2000 waivers), all trial data will be collected from clinical data entered in the EHR...Data collection is underway at all study sites with monthly uploads to the data portal.
This section of the Methods is a pragmatic example of which PRECIS-2 domain?

Primary Outcome

Setting

Follow-up

Flexibility (delivery)
Eligibility - Who is selected to participate in the trial?

Recruitment - How are participants recruited into the trial?

Setting - Where is the trial being done?

Organisation - What expertise and resources are needed to deliver the Intervention?

Flexibility - What measures are in place to make sure participants adhere to the intervention?

Flexibility - How should the intervention be delivered?

Primary outcome - How relevant is it to participants?

Primary analysis - To what extent are all data included?

Follow-up - How closely are participants followed-up?
Conclusions

• Trial components operate on a continuum of pragmatic -> explanatory
  – Decisions depend on goals of the investigators
  – Findings from pragmatic trials offer benefits of wider translatability and generalizability

• Start with the end in mind
  – Difficult to ‘save’ the trial *post hoc*
Feedback

[QR Code]