Design and Analysis Strategies for Embedded Pragmatic Clinical Trials

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Outlines

- Design of Pragmatic Clinical Trials
  - Study designs and randomization schemes
  - Endpoints and outcomes
  - Controls

- Data Analysis Considerations
  - Clustering
  - Preferred analytic models
  - Missing data
Methods for pragmatic trials

- Pragmatic trials do not require a completely different set of research designs, measures, analytic methods, etc.
- As always, the choice of methods depends on the research question.
- The research question dictates
  - the intervention, target population, and variables of interest,
  - which dictate the setting, research design, measures, and analytic methods.
- Randomized trials will provide the strongest evidence.
  - What kind of randomized trial depends on the research question and how the intervention will be delivered.
Design of Pragmatic Clinical Trials

Randomization Schemes

- Individual-randomized trial
  - Individuals randomized to study conditions, no interaction among participants after randomization
  - Most drug trials

- Individually randomized group-treated (IRGT) trial
  - The unit of randomization is the individual, but interventions are delivered in a group setting.
  - Many surgical trials
  - Many behavioral trials

- Partially nested randomized trial
  - Unbalanced design with clustering in only one study arm
  - Example: Participants in one arm receive a group meditation intervention, while those in the other arm receive individualized usual care
Design of Pragmatic Clinical Trials

Randomization Schemes

- **Group-randomized trial (GRT)**
  - The unit of randomization is a group or cluster, interaction among members of the same group before and after randomization, and measurement of outcomes is obtained among members of the groups or clusters
  - Parallel GRT
    - Separate but parallel intervention and control conditions throughout the trial, with no crossover
  - Stepped Wedge GRT
Design of Pragmatic Clinical Trials

Parallel GRT Designs

- **Group-randomized trial (GRT)**
  - Single factor and factorial designs: intervention vs. control
    - Some GRTs include stratification factors:
      - Multi-center GRTs cross Condition with Site.
      - Single-center GRTs often stratify on factors related to the outcome or to the ease of implementation of the intervention.
  - Time as a factor
    - Post-test only; Pre/post-test;
    - Additional discrete time intervals before and/or after intervention;
    - Continuous surveillance
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Parallel GRT Designs

- Group-randomized trial (GRT)
  - Examples:
    - **ICD-Pieces** (Parkland Intelligent e-Coordination and Evaluation System)
    - **TiME** (Time to Reduce Mortality in End-Stage Renal Disease)
    - **HiLo** (Higher vs. Lower Serum Phosphate Targets in Patients Undergoing Hemodialysis)
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Group-Randomized Trial

- **Balance across groups**
  - *A priori* matching and stratification
    - Either can be used if the investigators want to ensure balance on a potential source of bias.
    - *A priori* stratification is preferred if the investigators expect the intervention effect to be different across strata.
    - *A priori* matching is useful if the matching factors are well correlated with the primary endpoint.
    - Stratification or matching are difficult if there are multiple factors and a limited number of groups to be randomized.
  - Constrained randomization
    - Generate all possible allocations.
    - Identify those that are sufficiently well balanced across conditions on key covariates.
    - Choose one allocation at random to use for the trial.
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Randomization Schemes

- **Stepped-wedge group-randomized trial**
  - A one-directional crossover GRT that involves random and sequential crossover of groups/clusters from control to intervention so that eventually all groups are exposed to intervention.
  - The effect of intervention might be confounded with any underlying temporal trend.
  
  ![Diagram of stepped-wedge group-randomized trial](image)

- Example: LIRE (Lumbar Imaging with Reporting of Epidemiology)
Design of Pragmatic Clinical Trials

Stepped-Wedge Group-Randomized Trial

- Key methodological considerations
  - Confounding by time
    - Due to staggered implementation, time is correlated with intervention
    - Secular trend.
  - Contamination
    - Increased risk of within-group contamination: groups may implement intervention earlier or later than planned.
  - Time-varying intervention effects
    - Effects of intervention may vary depending on calendar time, or time since the intervention was introduced
  - Effect heterogeneity
    - Treatment effect may vary across groups, due to variation in quality of implementation, fidelity etc.
  - Complex correlations
    - Repeated measures on same group, and possibly same participants.
## Design of Pragmatic Clinical Trials

### Randomization Schemes

<table>
<thead>
<tr>
<th>Design</th>
<th>Unit of Randomization</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual-randomized trial</td>
<td>Individual</td>
<td>Individual level</td>
</tr>
<tr>
<td>Individually randomized group-treatment trial</td>
<td>Individual</td>
<td>Group level</td>
</tr>
<tr>
<td>Partially nested randomized trial</td>
<td>Individual</td>
<td>Group level for one intervention arm; Individual level for the other intervention arm</td>
</tr>
<tr>
<td>Group-randomized trial</td>
<td>Group</td>
<td>Group level</td>
</tr>
<tr>
<td>Stepped-wedge group-randomized trial</td>
<td>Group</td>
<td>Group level</td>
</tr>
</tbody>
</table>
Design of Pragmatic Clinical Trials

The Need for Different Designs

- An RCT is the best comparative design whenever...
  - Individual randomization is possible without post-randomization interaction.
- An IRGT is the best comparative design whenever...
  - Individual randomization is possible but there are reasons to allow post-randomization interaction.
- A GRT is the best comparative design whenever the investigator wants to evaluate an intervention that...
  - Cannot be delivered to individuals without risk of contamination.
- An SW-GRT is an alternative to a parallel GRT if...
  - It is unethical to withhold the intervention from any groups.
  - It is impossible to implement the intervention in many groups simultaneously.
  - External events are unlikely to affect the outcomes.
Design of Pragmatic Clinical Trials

Choice of Randomization Scheme

Is there a strong rationale for randomizing groups rather than individuals to study conditions?

- No
- Yes

Do participants receive their treatment in a group format or from a shared interventionist?

- No
- Yes

- RCT
- IRGT Trial

Is there a strong rationale for rolling out the intervention to all groups before the end of the trial?

- Yes
- No

- SW-GRT
- GRT

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*a* If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

*b* There may be logistical reasons to randomize groups or it may not be possible to deliver the intervention to individuals without substantial risk of contamination.

*c* There may be legitimate political or logistical reasons to roll out the intervention to all groups before the end of the trial.
Design of Pragmatic Clinical Trials

Endpoints and Outcomes

- Pragmatic outcomes:
  - Relevant for patients, physicians and clinical decision making
  - Mortality, morbidity, functional status, well-being and resource use
  - Generalizable, routinely collected outcomes
  - The inclusion of objective outcome measures

- Patient-reported outcomes (PROs):
  - Outcomes that represent subjective experiences, such as pain, symptoms and physical functions
  - Integration of PROs with EHR system
  - Other types of PROs, such as co-morbidities and hospitalizations, may also be obtained from the EHR or claims data
Design of Pragmatic Clinical Trials

Controls

- **Active controls**
  - Group intervention, such as education control, to provide social interaction with other participants and the practitioner.
  - Individual intervention, such as sham or simulated interventions.

- **Waitlist controls**
  - A contemporaneous group that has the promise of receiving the active intervention either after study completion or during a later follow-up period of the study

- **Usual care**
  - Variations among usual care
  - Potential drift in usual care over time
Data Analysis Considerations

- **Clustering**
  Clustering introduced by group-treatment in either one or both study arms must be accounted for.
  - In the sample size calculations:
    Intraclass correlation coefficient (ICC): a measure of how similar the outcomes of individuals within a cluster are likely to be, relative to those of other clusters.
  - Account for clustering in statistical analysis

<table>
<thead>
<tr>
<th>NUMBER OF PHYSICIANS PER TREATMENT ARM</th>
<th>INTRACLASS CORRELATION (RHO)</th>
<th>SAMPLE SIZE (TOTAL)</th>
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</thead>
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<td>278</td>
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</tbody>
</table>

*No physician effect.*

Data Analysis Considerations

- **ICC**
  Scott & Holt (1982) estimate the effect of the ICC as:
  \[
  \text{DEFF} = 1 + \left( m - 1 \right) \text{ICC}_y \text{ICC}_x
  \]
  - Design effect DEFF is the ratio of the variance as observed to the variance under simple random sampling.
  - ICC\(_y\) is the ICC for the dependent variable.
  - ICC\(_x\) is the ICC for the independent variable.

- **Sample size N = effective sample size × DEFF**

Data Analysis Considerations

- Preferred analytic models for GRTs with 1 or 2 time intervals:
  - **Mixed-model ANOVA/ANCOVA**
    - Extension of the familiar ANOVA/ANCOVA based on the General Linear Model
    - Fit using the General Linear Mixed Model or the Generalized Linear Mixed Model
    - Accommodates regression adjustment for covariates
    - Can not misrepresent over-time correlation
    - Can take several forms
      - Posttest-only ANOVA/ANCOVA
      - ANCOVA of posttest with regression adjustment for pretest
      - Repeated measures ANOVA/ANCOVA for pretest-posttest design
Data Analysis Considerations

- Preferred analytic models for GRTs with 3 or more time intervals:
  - Random coefficients models
    - Also called growth curve models
    - The intervention effect is estimated as the difference in the condition mean trends.
    - Random coefficients models allow for heterogeneity of those trends.
Data Analysis Considerations

- Individually Randomized Group Treatment Trials:
  - Analyses that ignore the ICC risk an inflated Type I error rate (cf. Pals et al., 2008; Baldwin et al., 2011).
    - Not as severe as in a GRT, but can exceed 15% under conditions common to these studies.
  - The solution is the same as in a GRT.
    - Analyze to reflect the variation attributable to the groups defined by the patterns of interaction.
    - Base df on the number of groups, not the number of members.
  - Mixed models are the most common approach.

Data Analysis Considerations

- **Missing Data**
  - Missing items or questionnaires in PROs such as measures for pain, physical function and quality of life
  - Loss to follow-up in trials with outcomes measured repeatedly over time
  - Inability or unwillingness of participants to meet appointments for evaluation
  - Missing data due to the lack of Medicare Advantage plan data being released with CMS claims
  - Impact on sample size/power
  - Assessment of the extent and nature of missingness
  - Missing data techniques
Resources of Information

- NIH Collaboratory
  Rethinking Clinical Trials®: A Living Textbook of Pragmatic Clinical Trials
  https://rethinkingclinicaltrials.org/
- Pragmatic and Group-Randomized Trials in Public Health and Medicine
  https://prevention.nih.gov/grt
- Mind the Gap Webinars
- Research Methods Resources Website
  https://researchmethodsresources.nih.gov/
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