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National Center for Complementary and Integrative Health

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

Design of Pragmatic Clinical Trials

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)

TiME

HiLo

A Pragmatic Trial Sponsored by the National Institutes of Health

Design of Pragmatic Clinical Trials

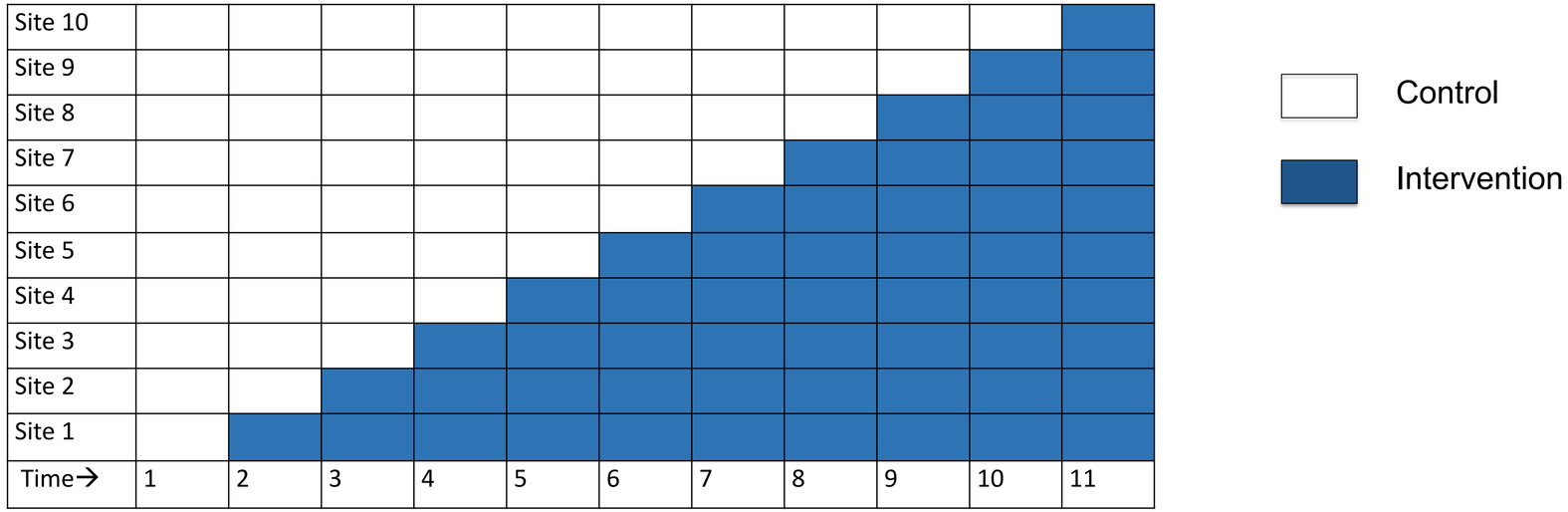
Group-Randomized Trial

- **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.

Design of Pragmatic Clinical Trials

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



  - 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

Design	Unit of Randomization	Intervention
Individual-randomized trial	Individual	Individual level
Individually randomized group-treatment trial	Individual	Group level
Partially nested randomized trial	Individual	Group level for one intervention arm; Individual level for the other intervention arm
Group-randomized trial	Group	Group level
Stepped-wedge group-randomized trial	Group	Group level

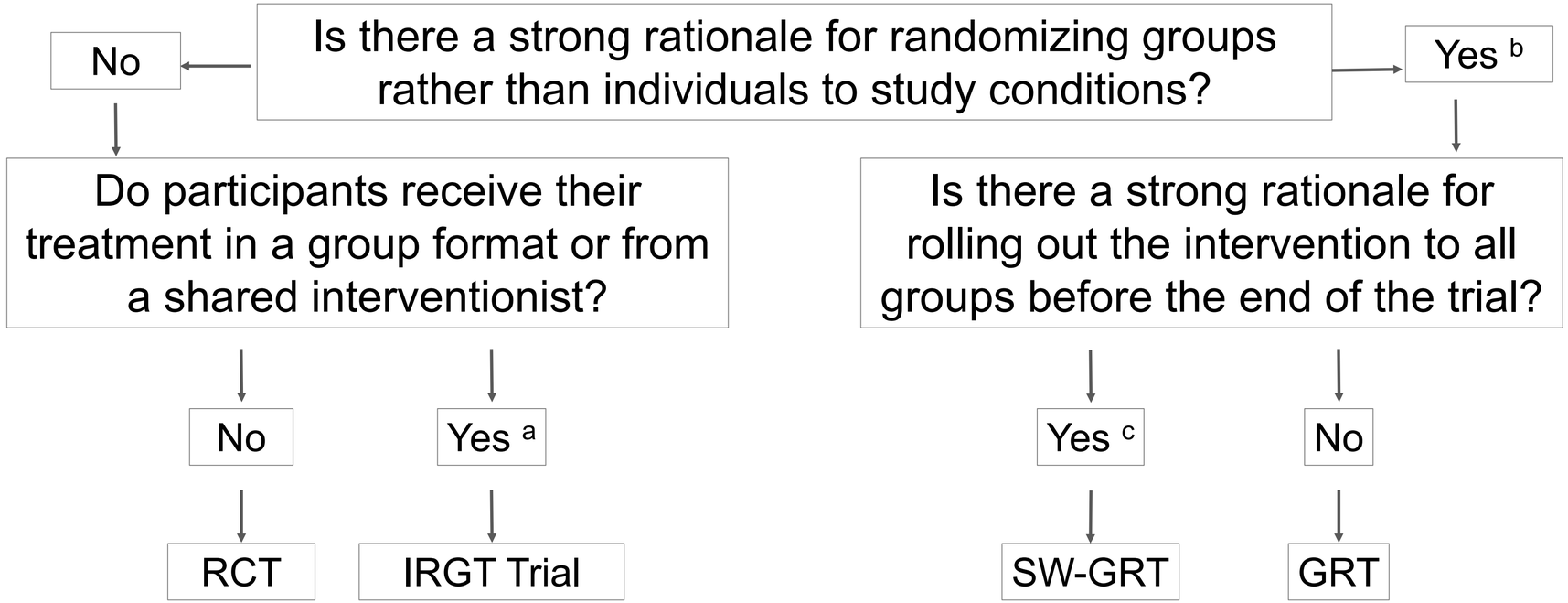
Design of Pragmatic Clinical Trials

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



[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 1

Relationship between Intraclass Correlation, Sample Size, and Number of Groups

NUMBER OF PHYSICIANS PER TREATMENT ARM	INTRACLASS CORRELATION (RHO)	SAMPLE SIZE (TOTAL)
4	0.0	200
	0.01	396
	0.02	∞
	0.03	∞
10	0.0*	200
	0.01	248
	0.02	320
	0.03	486
20	0.0*	200
	0.01	220
	0.02	246
	0.03	278

**No physician effect.*

From "Primer on Group Randomized Trials." *Effective Clinical Practice,* January/February 2001. 1:42-43.

Data Analysis Considerations

- ICC

  Scott & Holt (1982) estimate the effect of the ICC as:

$$DEFF = 1 + \left(m - 1\right) ICC_y ICC_x$$

  - 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

Scott AJ, Holt D. The effect of two-stage sampling on ordinary least squares methods. Journal of the American Statistical Association. 1982;77(380):848-54.

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.

Pals SL, Murray DM, et al. Individually randomized group treatment trials: a critical appraisal of frequently used design and analytic approaches. Am J Public Health. 2008;98(8):1418-24. PMID18556603.
Baldwin SA, Bauer DJ, et al. Evaluating models for partially clustered designs. Psych Methods. 2011;16(2):149-65. PMID21517179.

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

  https://prevention.nih.gov/education-training/methods-mind-gap
- Research Methods Resources Website

  https://researchmethodsresources.nih.gov/

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