Modern Study Designs for Pragmatic Translational Research:

Practical Guidance for Your Proposal

June 5, 2019
8:30 AM – 4:30 PM
Education 1 Room 1500
Anschutz Medical Campus

The overall learning objective of the conference is to prepare researchers to identify appropriate strategies for the design and implementation of pragmatic trials. Participants will explore common and developing pragmatic trial designs, analyze best fit for specific research questions, and navigate the resources available on the Anschutz Medical Campus.

CLUSTER RANDOMIZED | STEPPED WEDGE | SMART DESIGNS | BAYESIAN ADAPTIVE | Q&A

KEYNOTE
- **Scott Evans, PhD**
  Professor and Director of the Biostatistics Center, George Washington University

PLENARY ADDRESS
- **Alex Kaizer, PhD**
  Assistant Professor, Biostatistics & Informatics, University of Colorado Denver
- **David Vock, PhD**
  Assistant Professor, Biostatistics, University of Minnesota

EXAMPLES & DESIGNS
- Investigators will present exemplar case studies followed by biostatisticians highlighting corresponding methods, designs, and planning considerations
- Expert Panel (Q&A)

NETWORKING
- Breakfast & Coffee
- Lunch & Exhibition with campus reps & experts
- Networking with speakers & campus experts

ACCORDS
UNIVERSITY OF COLORADO
CHILDREN'S HOSPITAL COLORADO

Center for Innovative Design & Analysis
colorado school of public health

Welcome!

We are delighted that you have joined us for this conference on **Modern Study Designs for Pragmatic Translational Research**. Pragmatic trials refer to the broad range of studies that involve testing interventions in real-world settings. These trials have become increasingly popular due to potentially greater generalizability and external validity.

You may be considering a pragmatic trial for your next proposal if it includes one or more of the following:

- Diverse populations or multiple heterogeneous settings
- Participants can only be randomized at the group level (e.g., by hospital or practice)
- Interest in studying the implementation of an intervention
- The comparison is between two interventions that are real-world alternatives, rather than with a placebo or no treatment group
- Interest in studying multiple outcomes
- The outcomes may be measured as part of routine clinical care

Learning Objectives: The purpose of the conference is to allow you to:

- Gain an understanding about the defining characteristics and advantages/limitations of common and developing pragmatic trial designs
- Identify an appropriate pragmatic trial framework for a particular research question
- Obtain information about what resources are available on the University of Colorado Anschutz Medical Campus for developing, implementing, and analyzing a pragmatic trial

This workbook is aimed to support investigators interested in learning and applying the principles and methods for designing pragmatic translational research studies. The workbook provides a guide to researchers for applying the components of designing pragmatic research studies to their own work.

Sponsors: The Adult and Child Consortium for Health Outcomes Research and Delivery Science (ACCORDS), Center of Innovative Design & Analysis (CIDA)

Workshop planning committee:

Krithika Suresh, PhD
Research Assistant Professor, Department of Biostatistics and Informatics (B&I)
Biostatistician, ACCORDS Biostatistics Program

Bethany Kwan, PhD
Assistant Professor, Department of Family Medicine
Director, ACCORDS Education Program

Elizabeth Juarez-Colunga, PhD
Assistant Professor, Department of B&I
Director, ACCORDS Biostatistics Program

Bryan Ford
Program Coordinator, ACCORDS Education Program
Program Coordinator, ACCORDS D&I Program

Alex Kaizer, PhD
Assistant Professor, Department of B&I
Biostatistician, CIDA

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Agenda here (Will need to be added in the PDF version, Lisa at campus printing will do this. Bryan confirmed with her 5/17/19.)

Keynote and Plenary Speakers

Scott Evans, PhD

Professor & Director, *Biostatistics Center, George Washington University*

Dr. Scott Evans is a tenured Professor of Epidemiology and Biostatistics and the Director of the Biostatistics Center at George Washington University, and the Director of the Statistical and Data Management Center (SDMC) for the Antibacterial Resistance Leadership Group (ARLG). Dr. Evans is a recipient of the Mosteller Statistician of the Year Award, the Robert Zackin Distinguished Collaborative Statistician Award, and is a Fellow of the American Statistical Association (ASA), the Society for Clinical Trials (SCT), and the Infectious Disease Society of America (IDSA).

Professor Evans interests include the design, monitoring, analyses, and reporting of and education in clinical trials and diagnostic studies. He is the author of more than 100 peer-reviewed publications and three books on clinical trials including **Fundamentals for New Clinical Trialists**. He is the Director of the Statistical and Data Management Center (SDMC) for the Antibacterial Resistance Leadership Group (ARLG), a collaborative clinical research network that prioritizes, designs, and executes clinical research to reduce the public health threat of antibacterial resistance.

David Vock, PhD

Assistant Professor, Division of Biostatistics, University of Minnesota

Dr. Vock's research focuses on two major areas. The first is statistical methods development for electronic health data with a particular focus on development of machine learning techniques to handle censored data. Second, he works on novel methods for causal inference and estimation of dynamic treatment regimens (DTRs). This includes methods for novel clinical trials (e.g., SMART designs) used to test DTRs.

Dr. Vock also collaborates on projects related to transplantation, smoking cessation, cardiovascular disease, and infectious disease. He has expertise in chronic diseases, methods, causal inference, clinical trials, adaptive interventions, dynamic treatment regimes, semiparametric theory, machine learning, electronic health data, and transplantation.

Alex Kaizer, PhD

Assistant Professor, Division of Biostatistics, University of Colorado Denver - Anschutz

Dr. Kaizer is an Assistant Professor of Biostatistics and Informatics at the University of Colorado-Anschutz Medical Campus and a faculty member at the Center for Innovative Design and Analysis (CIDA). His research focuses on adaptive clinical trial design and methods to facilitate information sharing across multiple sources, with a focus on Bayesian methods for both.

Conference Presenters, Panel Members and Facilitators

Allison Kempe, MD, MPH

Director, ACCORDS

Professor of Pediatrics, Investigator, University of Colorado School of Medicine

Dr. Kempe is the Director for ACCORDS. She is a graduate of Oberlin College and the University of Colorado School of Medicine and did her residency at the Strong Memorial Hospital at University of Rochester. She then did a Robert Wood Johnson General Pediatrics Academic Development Fellowship at the University of Rochester, where she received a Master of Public Health degree. She has been a faculty member at the University of Colorado Denver since 1992 where she is now a tenured Professor of Pediatrics. Dr. Kempe has been involved in fellowship training and mentorship of junior faculty for twenty years and currently directs the SCORE Fellowship which trains surgeons and subspecialists to conduct outcomes research.

Miriam Dickinson, PhD

Professor, Senior Biostatistician, Department of Family Medicine

Dr. Dickinson is currently a biostatistician and Professor in the Department of Family Medicine, ACCORDS, Colorado Depression Center, and adjunct professor in the Department of Preventive Medicine and Biometrics at University of Colorado Denver. Her clinical research interests include mental health, chronic disease (diabetes, cardiovascular disease, hypertension), and immunization and she has numerous collaborations with investigators in these areas. As a biostatistician, she has focused on methodologic areas that are important to practice-based and community-based research. These efforts represent the important translational link from limited generalizability but critically important efficacy trials to real-world effectiveness trials in community and practice settings. However, many of these studies present difficult methodological challenges, such as practice-level randomization and longitudinal data with dropout.

Daniel Matlock, MD, MPH

Associate Professor, Department of Medicine

Director, Colorado Program for Patient Centered Decisions

Dr. Dan Matlock is an Associate Professor of Medicine in the Division of Geriatrics at the University of Colorado School Of Medicine. He is board certified in Internal Medicine, Geriatrics, and Palliative care. His research is aimed at fundamentally changing and improving how patients make decisions around invasive technologies. He is currently funded under an NIH career development award and three PCORI projects studying decision making among older adults making decisions around implantable cardioverter–defibrillators (ICD) and left ventricular assist devices.

Diane Fairclough, DrPH

Senior Biostatistician, ACCORDS Biostatistics & Analytics Core

Dr. Fairclough Received her doctoral degree in Biostatistics from the University of North Carolina and has held appointments at St. Jude Children's Research Hospital, Harvard School of Public Health, AMC Cancer Research Center and the University of Colorado Denver. She is a past President of the International Society for Quality of Life Research and has over 200 peer-reviewed publications. Dr. Fairclough's primary research interest is Quality of Life, outcomes in palliative/hospice care, and psychosocial sequelae of cancer and its therapy in pediatric and adult patients.

Erin Leister Chaussee, MS

Biostatistician, ACCORDS Biostatistics & Analytics Core

Ms. Chaussee is a PhD Candidate in Biostatistics here in the Department of Biostatistics & Informatics in the Colorado School of Public Health. Her dissertation research focusses on issues in stepped wedge design and analysis. She received an MS in Biostatistics from the University of Michigan in 2008 and has over 10 years of experience as a biostatistician. Prior to joining ACCORDS, Ms. Chaussee conducted statistical analyses of cohort studies on HIV-infected and affected populations in the United States, with a focus on treatment and outcomes in mothers and children. Since 2014, she has worked as a biostatistician on various research studies at ACCORDS, gaining experience in design and analysis of pragmatic trials. Ms. Chaussee is the primary statistical analyst of the DECIDE-LVAD trial (Dr. Daniel Matlock) that will be highlighted in this conference.

Elizabeth Juarez-Colunga, PhD

Director, ACCORDS Biostatistics and Analytics Core

Assistant Professor of Biostatistics, University of Colorado School of Public Health

Dr. Juarez-Colunga is an assistant professor in the Colorado School of Public Health. She received her BS in Applied Mathematics and MSc in Statistics in Mexico, and her doctoral degree in Statistics from Simon Fraser University in Canada. Elizabeth's areas of expertise and interest include: (i) analysis of data with dependencies at different levels including longitudinal and clustered data, (ii) analysis of repeated events data such as pulmonary exacerbations, (iii) joint modeling of multiple outcomes, and (iv) analysis of observational data. Through the ACCORDS program, she has been the lead biostatistician in several health outcomes research studies, including a smoking cessation trial, a tailored intervention to increase HPV vaccination in Latina women, and a pragmatic trial to assist weight loss in a low-income population. She has also served in PCORI grant review study sections including the Pragmatic Clinical Studies Study section and the Study Section of the Assessment of Prevention, Diagnosis, and Treatment Options.

Bethany Kwan, PhD, MSPH

Director, ACCORDS Education Program

Assistant Professor, Department of Family Medicine, University of Colorado School of Medicine

Dr. Kwan is an Assistant Professor in the Department of Family Medicine. She holds a PhD in social psychology from the University of Colorado Boulder (2010), a MS in Public Health from the University of Colorado Health Sciences Center (2005), and a BS in Chemistry and Psychology from Carnegie Mellon University (2001). She is a social health psychologist and dissemination and implementation scientist with research interests in chronic disease management and prevention and personalized behavioral healthcare in primary care settings. She is the principal investigator of a cluster randomized pragmatic trial funded by PCORI, comparing two models of diabetes shared medical appointments.

What are Pragmatic Trials?

Traditional randomized controlled trials are designed to answer questions under ideal conditions with strict controls to reduce heterogeneity (i.e., explanatory or efficacy trials), while pragmatic trials evaluate interventions under typical, real-world care conditions (i.e., effectiveness and implementation trials).

Key design elements of a pragmatic trial are:

1. **Real-world population.** The trial should enroll a largely unrestricted, generalizable population of patients that would receive the treatment in practice. This helps assess feasibility for delivering the intervention and provides generalizability to the target population.
2. **Real-world setting.** The trial should be conducted in regular care settings, and interventions are delivered by existing clinical personnel rather than the study team.
3. **Intervention and comparison arm.** The interventions should be adapted for delivery in real-world care and have the potential to be widely scaled and sustained. The comparison arm is often an active-control arm (e.g., usual care, another evidence-based intervention) rather than a placebo arm.
4. **Relevant outcome.** Pragmatic outcomes should be relevant to patients and inform healthcare treatment decisions. Outcomes are often measured using clinically-actionable instruments or obtained from existing data sources, such as electronic health records or medical claims.
5. **Non-standard randomization.** The trial may involve non-standard randomization (e.g., cluster randomization, uneven randomization ratios, randomization at different time points) to accommodate practical constraints, such as limited resources or contamination.

Key statistical considerations of a pragmatic trial are:

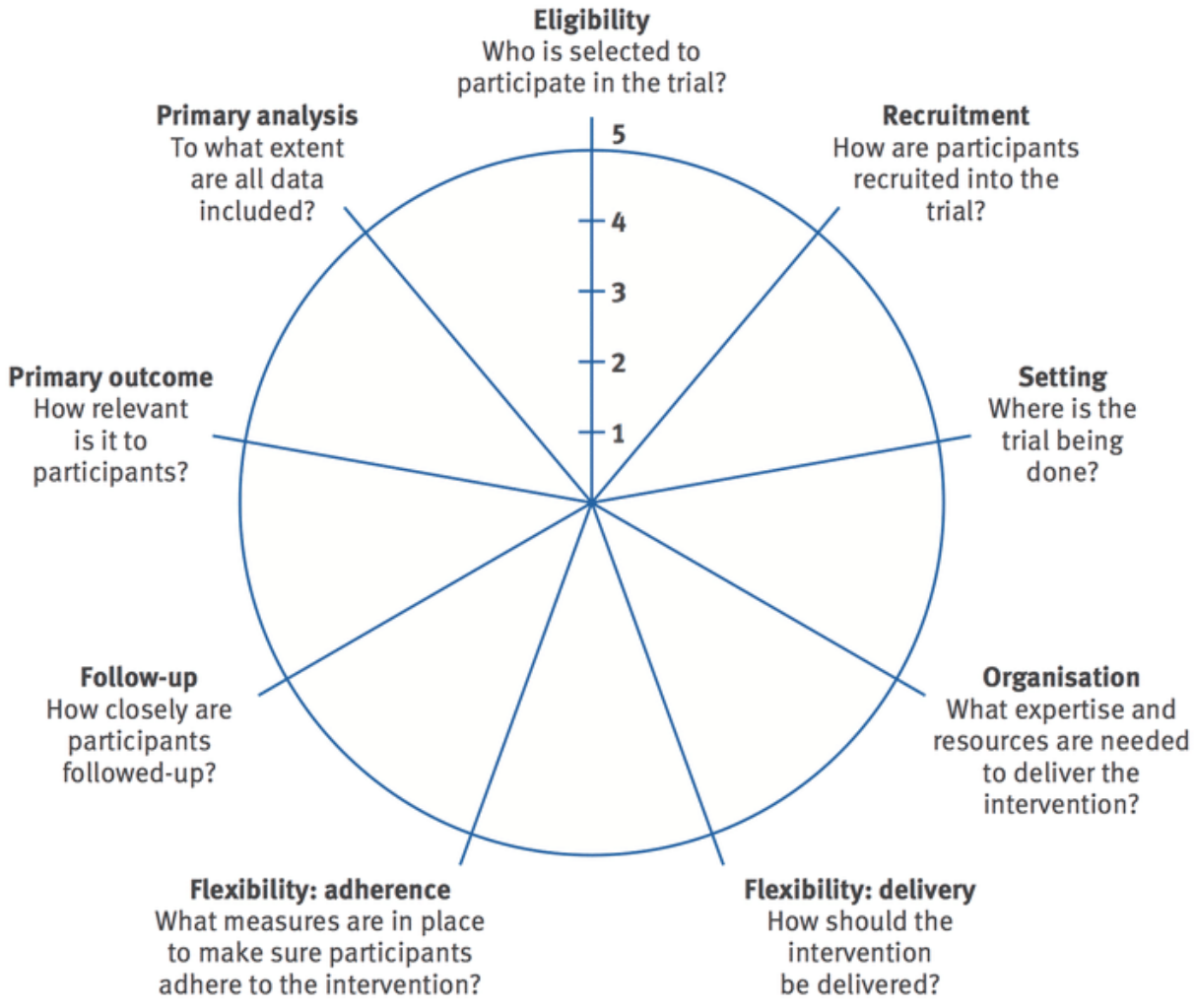
1. **Power.** Pragmatic trials often require more participants to achieve adequate statistical power to detect clinically meaningful effect sizes.
2. **Analysis.** Standard methods for analysis of individually randomized trials may not appropriate. Statistical analysis must incorporate the design features, such as clustering and temporal trends.

This workshop focuses on study design and statistical considerations in planning a pragmatic trial. For more information on pragmatic trials, including important topics such as stakeholder engagement and design features related to eligibility and recruitment, please visit:
http://www.crispebooks.org/PragmaticTrials/workbook-1627-1845R.html

PRECIS-2

Pragmatic-**E**xplanatory **C**ontinuum **I**ndicator **S**ummary – Version 2

The PRECIS-2 can be used a) as a *study planning tool*, b) to *report on studies*, and *c*) to *systematically review* interventions in the literature to select potential evidence-based practices to use. PRECIS-2 has nine domains reflecting key design features of clinical trials. Each element of a study design is given a rating between 1 and 5 on each domain relative to usual care, with 1 representing a very explanatory trial and 5 representing a very pragmatic trial. For interactive tools on the PRECIS-2 see: https://www.precis-2.org/



The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel.
Adapted from BMJ 2015;350:h2147

Keynote Address

Pragmatic Benefit:Risk Evaluation: Healthy Disruption for Clinical Trials

Scott Evans, PhD

Abstract:

Randomized clinical trials are the gold standard for evaluating the benefits and risks of interventions. However these studies often fail to provide the necessary evidence to inform practical medical decision-making. The important implications of these deficiencies are largely absent from discourse in medical research communities.

Typical analyses of clinical trials involve intervention comparisons for each efficacy and safety outcome. Outcome-specific effects are tabulated and potentially systematically or unsystematically combined in benefit:risk analyses with the belief that such analyses inform the totality of effects on patients. However such approaches do not incorporate associations between outcomes of interest, suffer from competing risk challenges, and since efficacy and safety analyses are conducted on different analysis populations, the population to which these benefit:risk analyses apply, is unclear.

This deficit can be remedied with more thoughtful benefit:risk evaluation with a pragmatic focus in future clinical trials. Critical components of this vision include: (i) using outcomes to analyze patients rather than patients to analyze outcomes, (ii) incorporating patient values, and (iii) evaluating personalized effects. Crucial to this approach entails improved understanding of how to analyze one patient before analyzing many. Newly developed approaches to the design and analyses of trials such as partial credit and the desirability of outcome ranking (DOOR), are being implemented to more optimally inform patient treatment.

Notes:

Application to Your Work

Learning happens best when applying new content to your own work. As the conference begins, please take a moment to identify at least one project you are working on that may be relevant to Pragmatic Trial Design. **Label the project(s) with a brief name** so that you can refer to them in the workbook throughout the workshop. For each project, brainstorm answers to each of the questions posed. You may come up with new ideas or refine existing ideas —feel free to come back and add to the list throughout the day.

My Project List

Project Name	Thought Questions
	• What intervention(s) do you want to test or compare? • What is the level of evidence for these intervention(s)? • To what extent are the evidence gaps primarily related to efficacy, effectiveness, and/or dissemination and implementation? • What is the relevant setting and population? • What outcomes matter to patients, health care providers, and systems?
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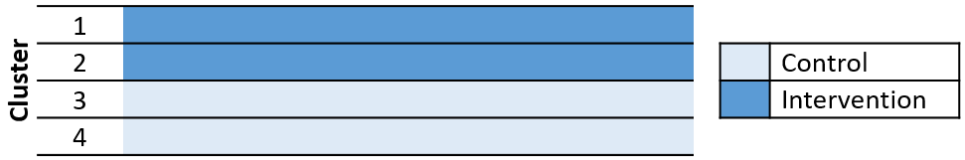
Cluster Randomized Trial

A **Cluster Randomized Trial (CRT)** is a trial in which clusters (e.g., hospitals, regions) rather than individuals are randomized to different intervention groups. A key implication of cluster randomization is that the responses of multiple individuals in the same cluster are usually positively correlated. Due to this positive intracluster correlation, advanced statistical methods (such as mixed models) must be considered for analysis.

Parallel Cluster Randomized Trial. Clusters are randomized to either the intervention or control arm at the start of the trial and remain in that arm for the remainder of the study.



The **advantages** of a CRT are that it is a simple design that is easy to implement. It is often considered when randomization at the individual level is not possible. Cluster randomization protects against contamination across intervention groups when patients are managed within the same setting or by the same provider. The **challenges** of a CRT are that it requires a large number of clusters to detect small effect sizes with adequate power. In a trial with a true control group, not all clusters will receive the intervention during the study.

Correlation in CRTs. An important implication in CRTs is that patients within a single cluster are often more likely to respond similarly due to physical, geographic, and social commonalities, and thus cannot be considered to contribute independent observations. This lack of independence results in a loss of statistical power compared to trials randomized at the individual level. To quantify how strongly patients in the same cluster resemble each other, the statistical measure **intracluster correlation coefficient (ICC)** is used. To achieve equivalent power to a patient randomized trial, standard sample size calculations must be inflated by a factor of

$$\mathbf{1} + (\boldsymbol{m} - \mathbf{1})\boldsymbol{\rho}$$

where $\boldsymbol{m}$ is the average cluster size, and $\boldsymbol{\rho}$ is an estimate of the ICC. This is referred to as a **design effect.**

Estimating ICC. ICC takes a value between 0 and 1, where an ICC closer to 1 indicates that there is high similarity between responses from individuals in the same cluster. ICCs for disease outcomes are generally less than 0.05. ICC can be estimated from other trials with similar populations and endpoints.

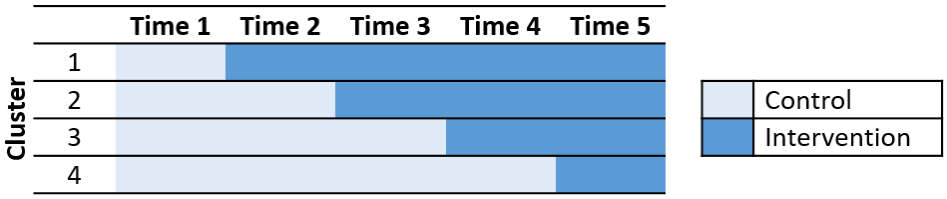
The **analysis** of data collected from a CRT must also account for clustering. Analyses at the cluster-level (i.e., using summary measures for each cluster) are generally not statistically efficient. Patient-level analysis can account for clustering using **generalized linear mixed models (GLMM)** and **generalized estimating equations (GEE)**. These modeling techniques also allow for the adjustment of both cluster-level and patient-level covariates.

Notes:

Stepped Wedge Design

A **Stepped Wedge (SW)** design is a type of crossover CRT, in which the different clusters cross over (switch treatments) at different time points. A SW study extends the traditional CRT so that every cluster provides both control and intervention observations, and thus somewhat acts as its own control.

The design includes a baseline time period where none of the clusters receive the intervention of interest. Then, at regular time periods (or "steps") one cluster (which can include multiple sites) is randomized to cross from the control to the intervention of interest. This process continues until all clusters have crossed over to receive the intervention, and the study ends with a time period in which all the studies receive the intervention.



Design considerations. When designing a SW study, the number of sites, number and length of time periods, and number of sites randomized at each time period must be determined. These are often chosen based on logistical considerations. The participants expected to meet eligibility criteria determine the number of patients per cluster per time period. There are possible variations to the traditional SW design, such as transition periods during which training is implemented and the cluster cannot be considered as exposed or unexposed. Power calculations for SW trials depend on these design considerations as well as on the intracluster correlation coefficient (ICC).

Advantages	Challenges
• Eventually all the clusters receive the intervention • Allows for control of external temporal trends • Allows for within-cluster comparisons and can have smaller sample size requirements than a cluster randomized trial • Implementation is staggered across sites, thus training can also be staggered and implementation can be more carefully observed	• Contamination can bias results • Requires all sites start and stop at the same time. Site dropout is a serious threat • Requires steady recruitment over time that is consistent with respect to patient characteristics • Potential for contamination during the cross-over between control and intervention phases with extended interventions and follow-up

Statistical analysis. Since the proportion of exposed clusters increases gradually over the study period, the unexposed observations will on average be from an earlier calendar time than the exposed observations. Thus, the analysis of SW studies must not only account for clustering, as with CRTs, but also needs to control for temporal trends. This can be achieved using a **generalized linear mixed model (GLMM)** with a random effect for cluster and a fixed effect for each time period. Extensions to these models can be considered to address issues such as varying temporal trends across clusters.

Notes:

Plenary Address

Adaptive Clinical Trials: From Basics to Bayesian

Alex Kaizer, PhD

Abstract:

Adaptive clinical trials come in a variety of designs, adaptable elements, and statistical frameworks. In this presentation we will start by defining what adaptive designs are and some of the basic elements that are "adaptable" according to the Food and Drug Administration. We will then transition into an exploration of how Bayesian methods are being used to empower adaptive clinical trials with some examples of existing designs and methods.

Notes:

Adaptive Trial Designs

An **Adaptive Trial (AT)** design is a clinical trial design that incorporates *prospectively planned* modifications to aspects of the design based upon accumulating data in the trial. The AT study design extends the "standard" design of trials to provide greater flexibility through a variety of mechanisms.

The Food and Drug Administration has released an updated draft guidance document in September 2018. It outlines the components incorporated in existing AT designs and provides high-level discussion of a variety of important considerations, many of which are highlighted on this worksheet.

Adaptive Design Element	Brief Description
Group Sequential Designs	Designs which allow for one or more prospectively planned interim analyses of trial data with prespecified criteria for stopping the trial, generally based upon evidence of efficacy or futility
Adapting the Sample Size	When uncertainty exists around the estimates used to power a study, an interim analysis can use accumulating data to re-estimate the sample size to ensure a trial has high power if the true magnitude was less than hypothesized but is still clinically meaningful
Adaptive Enrichment	A design which may adapt the patient population to a targeted subpopulation (usually through demographic characteristics or by genetic/pathophysiologic markers believed to be related to the mechanism of action) or continue to enroll the participants from the originally specified trial population
Adaptations to Treatment Arm Selection	Modification to the trial design that could add or terminate study arms, present in both early phase studies (e.g., dose-finding) and later phase studies (e.g., seamless designs and platform trials)
Adapting Patient Allocation	Also known as adaptive randomization (AR), the incorporation of methods to modify the randomization process that may be based on baseline covariates (i.e., the achieve "balance" in select covariates across study arms), response/outcome AR (i.e., attempting to randomize more participants to "effective" arms), or maintaining equal amounts of information when incorporating historic/supplemental data sources
Adapting Endpoint Selection	The ability to select one endpoint from a collection of potential primary endpoints when there is uncertainty about effect sizes across outcomes at an interim analysis, when done in FDA trials it involves extensive discussion and the review with the FDA Review Division
Adapting Multiple Features	The above elements can be utilized individually or may be combined within a single adaptive trial design (at the expense of increasing complexity that needs to be carefully and thoroughly evaluated)

Statistical analysis. The analyses used for adaptive trials are generally the same used in non-adaptive trials, but they incorporate the added complexity and potential statistical issues (e.g., multiplicity of tests) into the analysis plan. Both frequentist (e.g., p-values) and Bayesian (e.g., posterior or predictive probabilities) approaches are used, however some adaptive elements or designs may be infeasible under standard frequentist approaches. If Bayesian approaches are used, prior specification must be carefully considered and is generally done collaboratively based a combination of clinical, scientific, and statistical expertise and discussion. One of the most important considerations for AT designs is that any potential modification is specified *a priori* so that trial integrity can be maintained.

Adaptive trial planning and sample size. Many of the AT elements discussed on the previous page have complex underlying mathematical and statistical relationships that are not easily summarized or available in closed form formulas. To evaluate the needed sample size to maintain a specified type I error rate and desired power, extensive simulation studies are generally used. These simulation studies should evaluate a wide variety of scenarios and present the results for relevant operating characteristics, such as power, the type I error rate, expected sample size, expected calendar time, and bias in treatment effect estimates. Even when Bayesian approaches are used, the FDA specifies that potential designs be summarized using power and type I error rates, with type I error rates controlled at a prespecified target rate (e.g., α=0.05 for a two-sided test).

Additional Approaches and Considerations for Adaptive Trial Designs
Secondary Endpoints
Oftentimes a study will have secondary endpoints in addition to the primary endpoint(s). The AT element(s) chosen for the study can also have consequences for the analysis of secondary endpoints and these should be considered when evaluating different design options.
Safety Considerations
Adaptive design elements may affect the availability of safety information for the study arms (e.g., terminating early for efficacy may not provide sufficient information to evaluate risk vs. benefit) or the adaptive element may place participants at excessive risk (e.g., early phase dose-escalation studies that permit rapid escalation).
Design Changes Based on Information External to the Trial
Sometimes, other concurrently occurring research may identify important safety or outcome considerations that are important to your study. These changes are unplanned but should be critically evaluated in considering how to best move forward, where is may still be possible to modify the trial (e.g., excluding a subgroup at higher risk of severe adverse events instead of terminating the study to start over).
Incorporating Supplemental or Historic Information
Information or data external to a study or current analysis may be useful to incorporate to the analyses during an ongoing trial. Some designs may attempt to incorporate this information to increase the sample size of arms in the study, generally based on evaluating the exchangeability (i.e., equivalence) of the supplemental data with the current study data. Many approaches, that are primarily Bayesian, exist and include multi-source exchangeability modeling (MEMs), commensurate priors (CPs), power priors (PPs), and general Bayesian hierarchical models.
Master Protocols
Traditionally, researchers interested in evaluating multiple diseases, interventions, or both had to conduct a series of standalone trials comparing an intervention within the context of a single disease. The advent of master protocols, initially adapted in oncology trials, permits a single "master" protocol to facilitate inclusion of multiple diseases and/or interventions under a single trial structure and are known as basket, umbrella, or platform trials.
Seamless Designs
Similar to Master Protocols, these studies address a potential limitation in the traditional phases of research wherein each phase of a clinical trial were distinct and separate (e.g., Phase I, then Phase II, then Phase III, etc.). However, AT designs now exist which facilitate "seamless" transition between phases, and are often categorized as Phase I-II (e.g., dose finding, safety, and initial efficacy) or Phase II-III (e.g., identifying the optimal dose or outcomes and moving into confirmatory, large-scale trials for efficacy).

Summary. There are many exciting new trial designs based on adaptive elements. Some of the broad, general advantages and challenges of AT designs are summarized below to keep in mind when evaluating if an AT may be appropriate for your next study:

Advantages	Challenges
• Improved flexibility • More efficient use or allocation of available resources (e.g., financial or administrative) • Improved statistical efficiency that can provide greater statistical power to detect a true drug effect • Ethical considerations may be more readily addressed • Ability to answer broader questions, that may be refined as the trial progresses, relative to non-adaptive designs • Stakeholders may be more willing to support studies with adaptive elements because of the added flexibility	• Advanced and specific analytical methods needs to be used to avoid type I errors (i.e., identifying an ineffective intervention as effective) and control bias in estimates • Gains in efficiency generally represent a trade-off with other trial components (e.g., interim analyses may decrease *expected* sample size at the expense of an increase to the *maximum* sample size) • Logistics to ensure appropriate trial conduct and integrity • Adaptation may be limited by scientific or clinical constraints or make interpretation more challenging

Notes:

Plenary Address

Developing Adaptive Intervention Strategies Using SMART Designs

David Vock, PhD

Abstract:

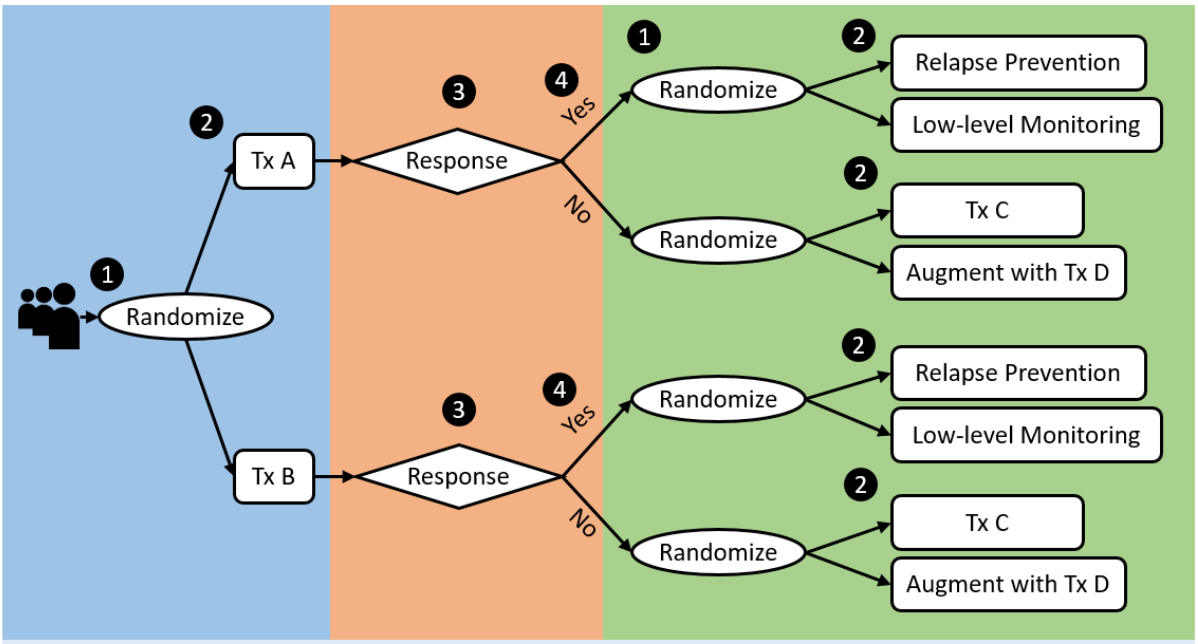
A sequential multiple-assignment randomized trial (SMART) is an experimental design that scientists can use to develop high-quality adaptive intervention strategies (AIS, also known as dynamic treatment regimes), a pre-specified treatment plan in which the type(s) or dosage/intensity of an intervention, the delivery of the intervention, or the monitoring schedule is repeatedly adjusted in response to new information collected about the individual. Specifically, a SMART design is a multi-stage trial design in which each stage corresponds to a critical decision where there is a scientific question about how best to intervene at that stage. Each participant progresses through the stages and can be randomly assigned to one of several intervention options at each stage. SMART designs allow one to answer a variety of questions concerning the development of an AIS. We highlight some of the common research questions and hypotheses and briefly discuss the appropriate analytical approaches to test these hypotheses. We contrast a SMART design with other experimental designs that could be used for developing or for evaluating different AISs. We conclude by dispelling common misconceptions concerning AISs and SMART designs and reviewing future research directions.

Notes:

Sequential Multiple Assignment Randomized Trial (SMART)

SMART is an innovative design for pragmatic trials comparing adaptive interventions. Adaptive interventions can allow clinical settings or patients who do not respond to an initial treatment strategy to receive an augmented or new intervention. A SMART is not an adaptive intervention itself, but instead is a trial with multiple embedded adaptive interventions that can be compared. It is an adaptive multi-stage randomized trial design, where each participant is randomized to an initial treatment and then may move through multiple stages of treatment depending on their response, characteristics or behaviors observed during previous treatments. Each stage in a SMART corresponds to a critical treatment decision and participants are randomly (re)assigned to a treatment option. By randomizing participants multiple times, researchers can assess the effectiveness of treatments at each stage.

The purpose of SMARTs is to build empirically supported adaptive interventions. SMARTs allow for the testing of the tailoring variables, which are used to trigger a change in treatment, and interventions in the same trial. This allows for the best decision rules to be developed based on research rather than a priori decisions. Data from a SMART study can then be used to design an adaptive intervention in which patients are not randomized; instead, their treatments change based on the intervention's decision rules. Q-learning methods can also be applied to SMART design data to discover optimal treatments.



First, all participants are randomized. One group receives treatment A and the other treatment B.

As soon as a participant meets the condition for non-response they are re-randomized. If after a specific period of time they do not meet the criteria for non-response they are classified as responsive.

Participants who were non-responsive were randomized to receive either treatment C or to have their current treatment augmented by treatment D. Participants who responded to the initial treatment were randomized to either relapse prevention or low-level monitoring.

1. **Decision stage.** Begins with a decision concerning treatment
2. **Treatment options.** Correspond to different treatment types, dosages, or delivery options
3. **Tailoring variables.** Information about the individual to be used in making treatment decisions (e.g., nonresponse, side effects)
4. **Decision rule.** Links the tailoring variables to the most appropriate treatment options for the patient.

Notes:

Is a Pragmatic Trial Right for You?

No study is completely pragmatic/explanatory. Use the following questions to identify where your study falls on the explanatory-pragmatic trial continuum. If the majority of your answers lie towards the right-side of the spectrum, a pragmatic trial may be more appropriate for your research.

What is the research question of interest?

Interested in: Can the intervention work (efficacy) and in testing hypotheses under ideal conditions.

Interested in: Does the intervention work (effectiveness) and comparing intervention strategies in usual care settings.

The outcome is biologically meaningful.

The outcome is meaningful for decision-making in routine clinical practice.

Why are you interested in studying this treatment?

Want to assess cause and effect of the intervention.

Want the results to inform decision makers.

Interested in comparing a new intervention to a control.

Interested in comparing an intervention with the current standard of care or another evidence-based intervention.

How will the study be conducted?

The protocol will be rigidly followed to minimize variation and the effect of extraneous variables.

The protocol will reflect usual care settings to maximize generalizability

Who will participate in the study?

Selective inclusion criteria will be defined and participants will potentially be recruited.

Broad inclusion criteria will include those that are encountered in routine clinical practice.

Adapted from: https://rwe-navigator.eu/use-real-world-evidence/generate-real-world-evidence/study-design-pragmatic-trials/

Designing Your Pragmatic Trial

Use the following questions, to help guide you when writing up a proposal for a pragmatic trial and to help determine an appropriate trial design. **Contact a biostatistician early to discuss potential study designs for your research proposal.**

The research question of interest is...
Tests whether the intervention is effective in routine clinical practice.
E.g., What is the best dose of aspirin to prevent a heart attack in patients with heart disease?

The setting of interest is…
Routine care settings. *E.g., Primary care, community clinics, hospital units, health systems*

The population of interest is...
Broad selection criteria. *E.g., People living with heart disease or hypertension.*

The interventions that will be compared are...
Compares two or more real-world treatments. *E.g., 81 mg vs. 325 mg dose of aspirin.*
If there are more than two treatments being compared, consider a CRT or a patient randomized trial instead of a SW.

Has efficacy (and safety) of the intervention been established in other trials?
Discuss safety and feasibility of implementing the proposed treatment. Note known effect sizes and ICCs where possible.

The randomization unit is…
Identify if patients will be randomized at the patient or cluster level, and what level data will be collected.

Is contamination an issue?
Contamination occurs when participants assigned to one intervention receive elements of another intervention.
Can it be resolved by increasing the cluster size/moving up to a higher level (*e.g., health system vs. hospital*)?

Is the recruitment rate likely to be constant across time?
If no, consider a CRT rather than a SW to avoid time periods during which recruitment is low.

Is it feasible to implement the intervention for all randomized units at the same time?
If no, consider a SW rather than a CRT to allow for the implementation at more clusters at different time points.

What sample size do I need?

Another study design consideration is what sample size is required to detect a clinically meaningful effect. Here we present the sample size calculation for a simple CRT and SW, but extensions to these designs, such as variable cluster sizes and transition periods, may also be factored into the power calculation. Contact a biostatistician before finalizing your study design to ensure that there is enough power to implement such a study to detect the desired effect size.

Specify a priori:

- Desired statistical power (e.g., 80%) and significance (e.g., 5%)
- Minimally important effect size
- Continuous outcome: Standard deviation (σ)
- Binary outcome: Control arm proportion

Additionally required for a CRT:

- ρ: Anticipated intraclass correlation coefficient (ICC)
- m: Average cluster size (i.e., # of patients in each cluster)

Additionally required for a SW:

- t: Number of time periods
- ρ: Anticipated intraclass correlation coefficient (ICC)
- m_c: Average cluster size (i.e., # of patients per cluster per time period)

Design Effect for a parallel CRT:

$$D_{eff} = 1 + (m-1)\rho$$

Design Effect for a balanced complete SW:

$$D_{eff} = (t+1)\frac{1+\rho(tm_c+m_c-1)}{1+\rho\left(\frac{tm_c}{2}+m_c-1\right)} \times \frac{3(1-\rho)}{2\left(t-\frac{1}{t}\right)}$$

Number of required clusters:

$$k = \frac{n_{ind} \times D_{eff}}{m}$$

where n_{ind} is the total sample size required under individual randomization using the a priori information.

Number of required clusters:

$$k = \frac{n_{ind} \times D_{eff}}{(t+1)m_c}$$

where n_{ind} is the total sample size required under individual randomization using the a priori information.

Considerations when comparing CRT and SW:

- For large ICCs, a SW study has more power than a CRT with a fixed sample size
- When the design is constrained by a small number of clusters, the SW provides higher power than a parallel CRT design. However, designs with too few clusters have increased risk of type I and II errors and decreased generalizability.
- Relative to CRTs, power for a SW study is less sensitive to differences in ICC
- For a given number of clusters, a SW design where each cluster crosses over to the intervention at its own step has optimal power

Notes:

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Notes:

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