What is ACCORDS?

Adult and Child Center for Outcomes Research and Delivery Science

ACCORDS is a ‘one-stop shop’ for pragmatic research:

- A multi-disciplinary, collaborative research environment to catalyze innovative and impactful research
- Strong methodological cores and programs, led by national experts
- Consultations & team-building for grant proposals
- Mentorship, training & support for junior faculty
- Extensive educational offerings, both locally and nationally

ACCORDS Upcoming Events

October 16, 2023 AHSB 2200/2201, Zoom	**Statistical Methods for Pragmatic Research** *Mediation Methods* *Presented by:* Heather Smyth, PhD, MA (CIDA)
November 1, 2023 AHSB 2200/2201, Zoom	**Ethics, Challenges, & Messy Decisions in Shared Decision Making** *Ethical Issues in Shared Decision Making* *Presented by:* Drs. Laura Scherer, Matthew Wynia, and Dan Matlock
November 9 & 16, 2023 9:00-3:00pm MT Zoom	**Overview of Dissemination and Implementation (D&I) Science Workshop** *Lead facilitators:* Tina Studts, PhD and Borsika Rabin, PharmD, PhD
November 20, 2023 AHSB 2200/2201, Zoom	**Statistical Methods for Pragmatic Research** *Randomization-based Inference for Cluster Randomized Trials* *Presented by:* Dustin J. Rabideau, PhD (Massachusetts General Hospital)
December 6, 2023 AHSB 2200/2201, Zoom	**Ethics, Challenges, & Messy Decisions in Shared Decision Making** *Breast Cancer and Quality of Life* *Presented by:* Sarah Tevis, PhD
December 18, 2023 AHSB 2200/2201, Zoom	**Statistical Methods for Pragmatic Research** *Presented by:* Maren Olsen, PhD (Duke)

*all times 12-1pm MT unless otherwise noted

Statistical Methods for Pragmatic Research

2023-2024 Seminar Series

Presented by:
Kathryn Colborn, PhD

Considerations for the Design and Analysis of Pragmatic Trials

Considerations for the Design and Analysis of Pragmatic Trials

Katie Colborn, PhD, MSPH

ACCORDS Biostatistics and Analytics Core Lead

Division of Healthcare Policy and Research, Department of Medicine

University of Colorado Anschutz Medical Campus

Outline

- Overview of pragmatic research
- Working with a statistician to design your study and analytic plan
- Trial designs and tradeoffs
- Statistical Methods
- ACCORDS Biostatistics and Analytics Core

Overview of Pragmatic Research

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Pragmatic Research

- "Pragmatic trials are designed to answer the question of whether a program works under usual conditions, compared to explanatory trials that answer the question if an intervention works under ideal conditions."[1] ~ Russ Glasgow
- Guidelines for design:
  1. Research questions and outcomes must be important to stakeholders (e.g., patients, policy makers, clinicians)
  2. Research is conducted in multiple real-world, often heterogenous, settings
  3. Few exclusion criteria – participants are representative of those within that setting
  4. Comparison group(s) typically receive standard of care

[1]Glasgow R. What Does It Mean to Be Pragmatic? Pragmatic Methods, Measures, and Models to Facilitate Research Translation. 2013. Health Education & Behavior 40(3) 257–265

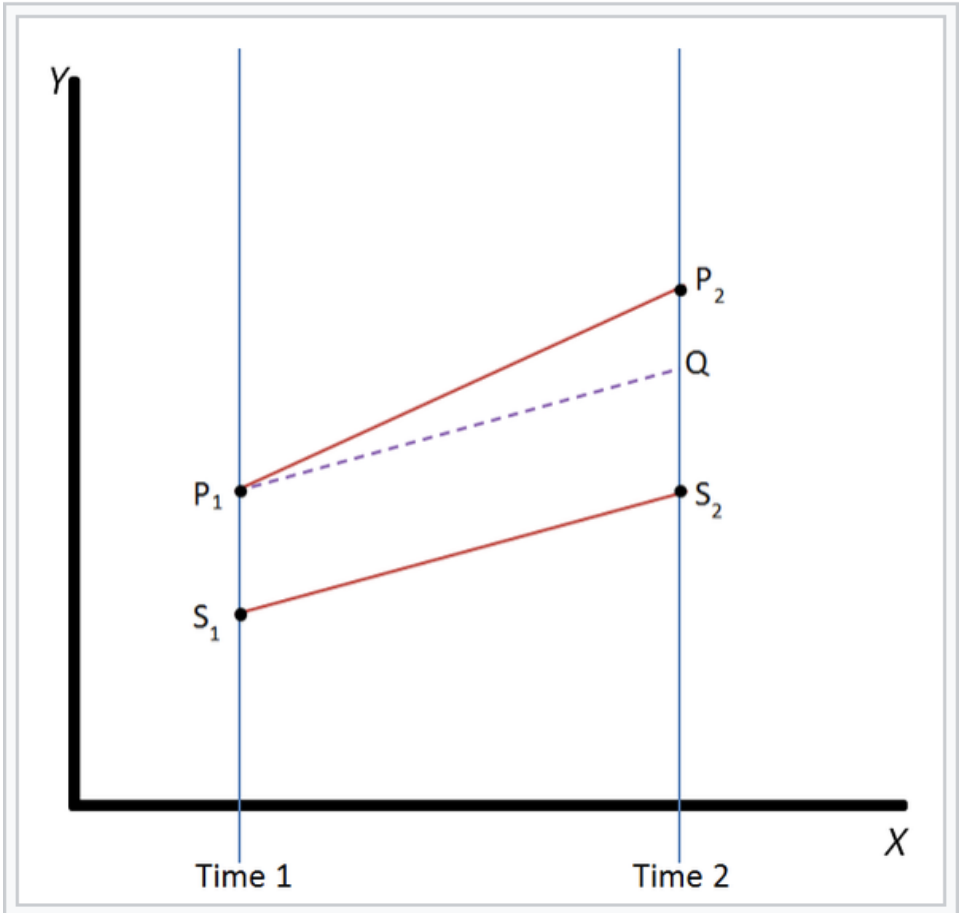
Outcome Measures

- Pragmatic Research Outcome Measure Requirements:[2]
  - Important to stakeholders
  - Low burden for participants and study team
  - Actionable (clear immediate value)
  - Reliable and valid over time (short reporting periods, large effect sizes)
- Statistician's Perspective:
  - Large effect size
  - Low attrition
  - Proximal to the intervention
  - Confounding can be mitigated

[2]Glasgow R, Riley W. Pragmatic Measures: What They Are and Why We Need Them. 2013. American Journal of Preventive Medicine 45(2) 237-243

Outcome Measures Continued

- Primary vs. Secondary
  - Power the study on your primary outcome
  - Minimize the number of outcomes that are collected outside of routine care
  - Adjust for multiple comparisons
- Cross-sectional vs. Longitudinal
  - Trajectory (time series)
  - Difference-in-differences (pre-post)



Designing Your Intervention

- Stage of scientific maturity
- Pragmatic trials typically fall under stages 3, 4, or 5 (i.e., real-world settings)
- Setting: single site, multiple sites
- Participants: providers, patients, caregivers

NIH Stage Model

Stage 0	Basic Science
Stage 1	Intervention generation, refinement, pilot testing
Stage 2	Efficacy testing
Stage 3	Efficacy testing in real-world setting
Stage 4	Effectiveness research
Stage 5	Dissemination and implementation research

Choosing the Right Control Group

- Typically, usual care or slightly augmented usual care
- Enhanced usual care provides straightforward inference
  - e.g., ensuring the control group receives the same number of visits at similar time points as the intervention arm
- Ideally randomized at the individual participant level
- Randomization may need to be done in clusters (e.g., within sites, clinics, providers) to avoid contamination or because the intervention is at that level
- Ethics: staggered randomization may be more ethical (but complicates implementation and statistical analysis)
- Be careful of "Hawthorne effect"

Working with a Statistician

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Statistical Analysis Plan Development

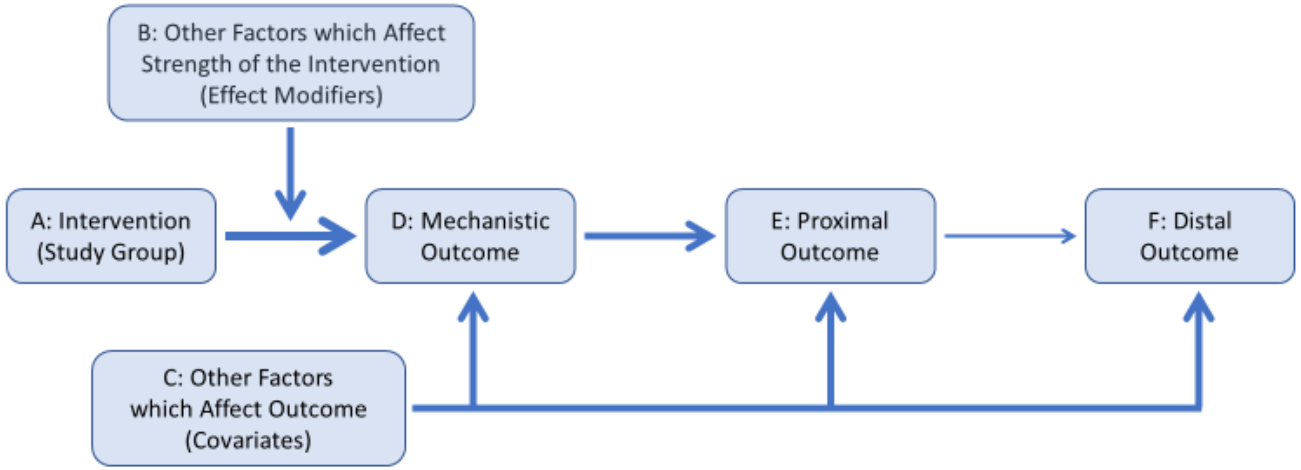
- It requires a phone/video conversation or in-person meeting not an email
- What to bring to your first meeting:
  - Specific Aims Page
  - Diagram of study design and data collection schedule
  - Primary and secondary outcomes
    - How are they collected/measured?
    - Variable types: numerical, counts, binary, categorical
  - Diagram of conceptual model

Conceptual Model

- Graphical representation of the theories, beliefs, and assumptions in a research study
- Shows cause-and-effect relationships between dependent and independent variables, confounders, and other factors, such as moderators or mediators

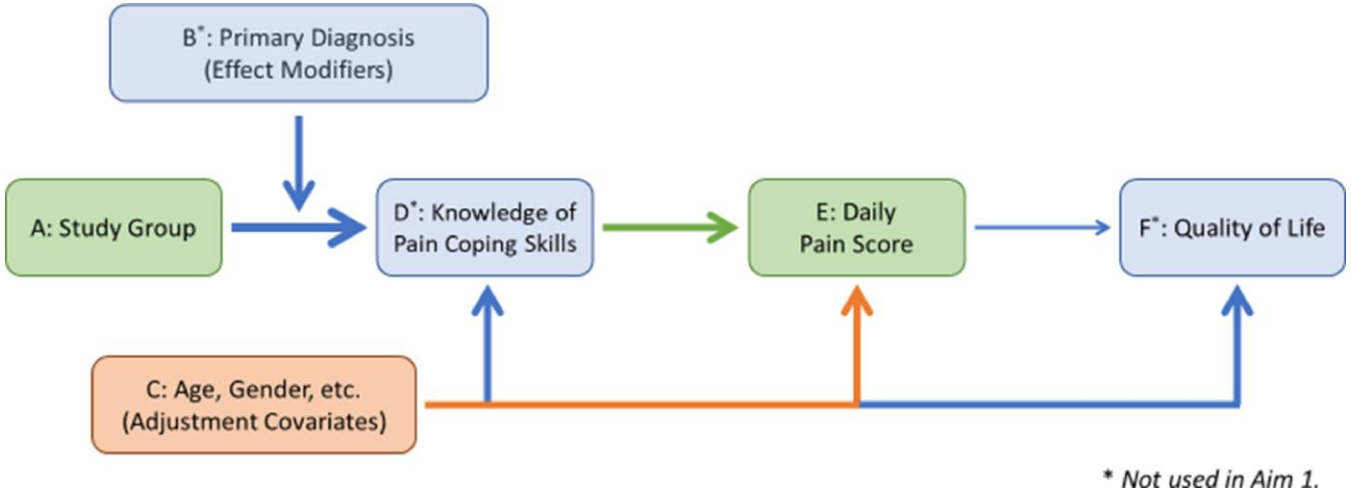
A Statistician's Conceptual Framework

- Box A: primary predictor (i.e., intervention group)
- Box B: factors that affect strength of the intervention effect
- Box C: factors that affect the outcome (i.e., covariates)
- Box D-F: outcome variables arranged by location on the causal pathway from intervention to outcomes



Samsa G, Colborn K, Olsen M, Pomann GM, Grambow S, Neely M, Troy J. *A Visual Tool to Help Develop a Statistical Analysis Plan for Randomized Trials in Palliative Care*. J Pain Symptom Manage. 2023 Jan;65(1)

Example SAP



- "Aim 1: (primary) Compare the pain coping intervention to usual care on the primary outcome of daily pain score at three months.
- Aim 2: (secondary) Determine whether the efficacy of the pain coping intervention (on daily pain score at three months) depends on primary diagnosis (i.e., cancer versus non-cancer).
- Aim 3: (exploratory) Compare the pain coping intervention to usual care on the exploratory outcome of quality of life at three months."

Example SAP Continued

- "Aim 1 will be addressed using a t-test with study group as the (binary) predictor variable and daily pain score at three months as the (continuous) outcome. Recognizing that the t-test is a special case of a linear regression model with study group as its only predictor, this primary (unadjusted) analysis will be supplemented by a linear regression model with study group as the primary predictor, the covariates age (continuous), gender (binary) and primary diagnosis (binary) as adjustment variables, and daily pain score at three months as the outcome. These analyses will be preceded by an exploratory mechanistic analysis which compares the study groups on the (continuous) outcome of knowledge of pain coping skills."

Example study

JOURNAL OF PALLIATIVE MEDICINE
Volume 22, Number S1, 2019

DOI: 10.1089/jpm.2019.0130

A Multicenter, Randomized Controlled Trial of Perioperative Palliative Care Surrounding Cancer Surgery for Patients and Their Family Members (PERIOP-PC)

Rebecca A. Aslakson, MD, PhD,[1,2] Shivani V. Chandrashekaran,[1] Elizabeth Rickerson, MD,[3,4] Bridget N. Fahy,[5] Fabian M. Johnston, MD, MHS,[6] Judith A. Miller,[7] Alison Conca-Cheng,[8] Suwei Wang, PhD,[1] Arden M. Morris, MD, MPH,[9] Karl Lorenz, MD, MSHS,[1,10] Jennifer S. Temel, MD,[11] and Thomas J. Smith, MD[12]

SAP template

PERIOP-PC ANALYTIC PLAN FOR PRIMARY PAPER
January 25, 2022
Primary author: Rebecca Aslakson
Analysts: Katie Colborn, Shelby Smith

Study population: Patients
Analytic plan: Evaluate differences in QOL by treatment arm using t-tests at 3 months postop.
Outcomes: PROMIS physical z-score, PROMIS mental z-score, PROPr, FACIT-Pal, FACT-G

TABLES
Table 1. Demographic characteristics of patients by treatment arm. Include some clinical characteristics to evaluate if the two arms are balanced.

Characteristic	**Treatment [random]**	**Control**	**P-value**
Age [age]	Mean (SD)	Mean (SD)	
Sex [sex]	N (%)	N(%)	
Ethnicity [ethnicity]	Cat.	Cat.	
Cancer Type [cancer_type]	Cat.	Cat.	

*P-values will be from t-tests or chi-square tests

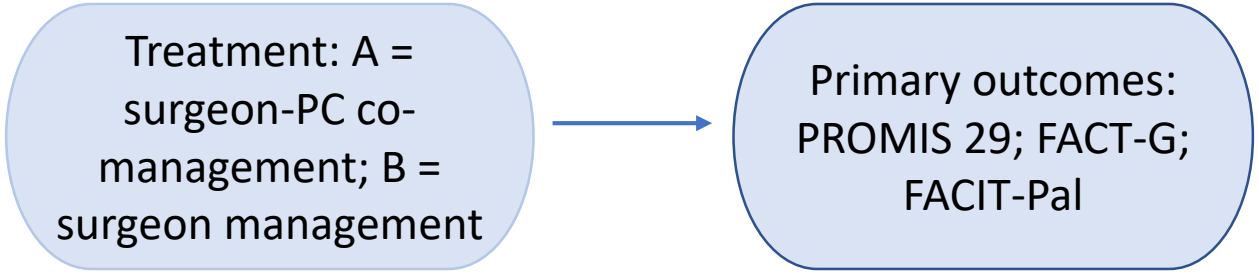
Table 2. Differences in primary and secondary outcomes by treatment group at 3 months survey.

QOL measure	**Treatment**	**Control**	**P-value**
PROMIS 29 [promis_1…promis_29]	Mean(SD)	Mean(SD)	
Facit-Pal [gs_1…]	Mean(SD)	Mean(SD)	
Fact-G	Mean(SD)	Mean(SD)	

*P-values will be from t-tests at 3 months

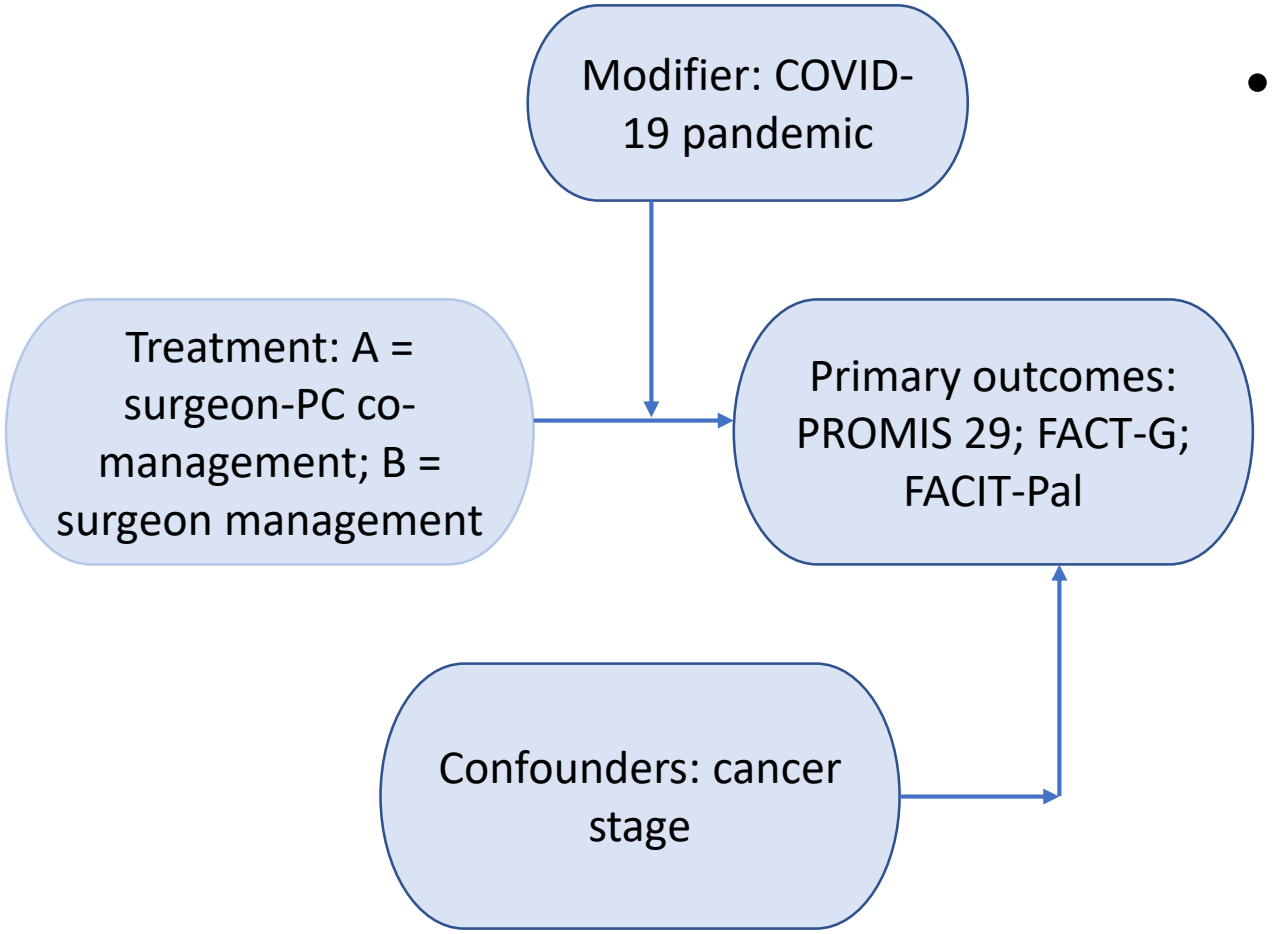
FIGURES
Figure 1. CONSORT diagram
Figure 2. Longitudinal box plots of primary outcomes by treatment arm across time points.

Example graphical SAP



- Statistical analysis:
  - We will compare the PROMIS physical and mental health z-scores, and PROPr, FACT-G, and FACIT-Pal scores between the two arms at 3 months postop using t-tests.

Example graphical SAP: alternative



- Statistical analysis:
  - We will compare the PROMIS physical and mental health z-scores, and PROPr, FACT-G, and FACIT-Pal scores between the two arms at 3 months postop using multiple regression models. These models will include a binary factor for treatment, a categorical factor for cancer stage, a binary factor for pre vs. post COVID-19 pandemic, and an interaction between COVID-19 pandemic and treatment.

Trial Designs and Tradeoffs

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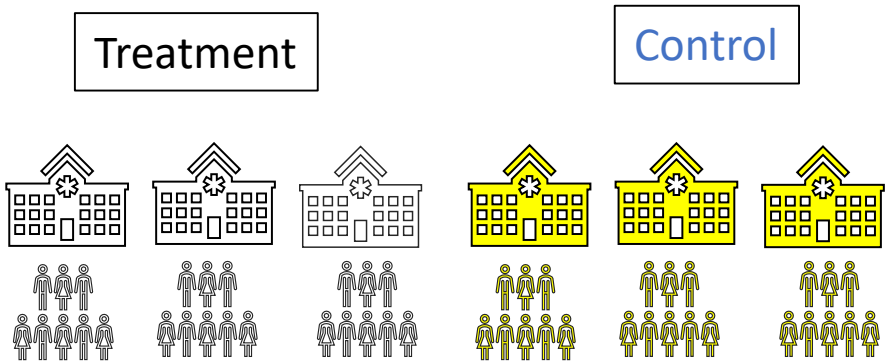
Randomized Controlled Trial (RCT)

- RCT design is ideal - balances confounders between treatment and control groups
- *t*-test or chi-square test should be sufficient for analysis
- Use regression or more complex methods if hypothesis includes interaction, mediation, pre-post

Cluster Randomized Trial (CRT)

- **Very common in pragmatic research**
- Some interventions need to be randomized to clinics or hospitals (e.g., contamination potential, feasibility, etc.)
- Power is optimized with more smaller clusters compared to fewer larger clusters
- Individual-level data analysis may require adjustment for confounders



Intracluster Correlation (ICC)

- Measure of relatedness of individuals within a cluster
- When it is present, it reduces power because the observations cannot all be considered independent

Design Effect

- For a CRT, you should apply a "design effect" (DE) when estimating sample size
- This estimates the "effective sample size" (ESS), when ICC is present:

$$DE = 1 + (m - 1)\rho$$

$$ESS = \frac{km}{DE}$$

- Above, k is the number of clusters, m is the number of individuals per cluster, and ρ is the ICC

ESS example

- Let's say we want to recruit 360 patients into our study. We could enlist 3 sites, and 120 patients from each site. Using the equations on the previous slide, for four values of ICC: (0, 0.01, 0.02, 0.2), the ESS would be 360, 164, 107, and 15, respectively.
- If we instead recruited 36 patients each from 10 sites, we would have ESS: 360, 267, 212, and 45, for the same values of ICC.
- **More clusters with fewer patients per cluster yields a larger ESS**

Types of CRTs

- Parallel CRT
- Crossover
- Stepped Wedge

	Parallel			Crossover			Stepped Wedge					
	Time			Time			Time					
Site	1	2		1	2		1	2	3	4	5	6
1	C	T		T	C		C	T	T	T	T	T
2	C	T		T	C		C	T	T	T	T	T
3	C	T		T	C		C	C	T	T	T	T
4	C	T		T	C		C	C	T	T	T	T
5	C	T		T	C		C	C	C	T	T	T
6	C	C		C	T		C	C	C	T	T	T
7	C	C		C	T		C	C	C	C	T	T
8	C	C		C	T		C	C	C	C	T	T
9	C	C		C	T		C	C	C	C	C	T
10	C	C		C	T		C	C	C	C	C	T

Issues with Stepped Wedge

- Kotz, Daniel, et al. "Use of the stepped wedge design cannot be recommended: a critical appraisal and comparison with the classic cluster randomized controlled trial design." Journal of clinical epidemiology 65.12 (2012): 1249-1252.

- Kotz, Daniel, et al. "Researchers should convince policy makers to perform a classic cluster randomized controlled trial instead of a stepped wedge design when an intervention is rolled out." Journal of clinical epidemiology 65.12 (2012): 1255-1256.

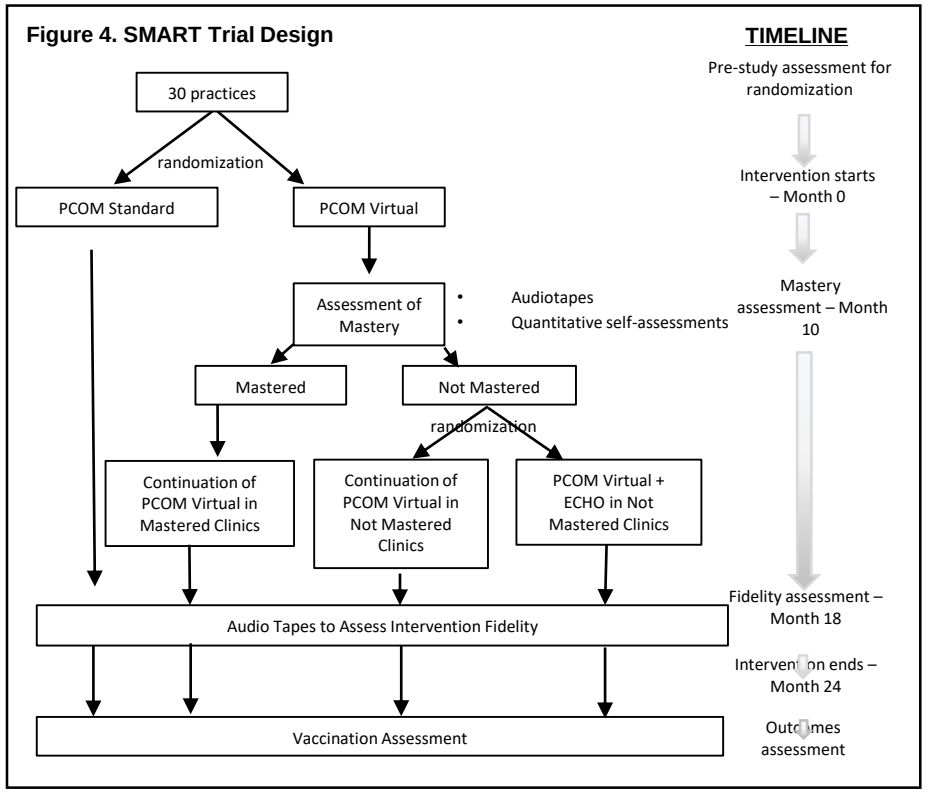
- Kotz, Daniel, et al. "The stepped wedge design does not inherently have more power than a cluster randomized controlled trial." Journal of clinical epidemiology 66.9 (2013): 1059-1060.

Adaptive designs

- Sequential Multiple Assignment Randomized Trial (SMART)
- Learn-As-you-GO (LAGO)
- Dynamic Treatment Regimes (DRT)
- Require larger sample size than parallel RCT

https://academic.oup.com/biostatistics/article/21/3/432/5149691

https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-018-1017-7



Statistical Models

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Conditional Models

- Generalized linear mixed models (GLMMs)
  - Generally, include one random effect to account for clustering (may have more than one)
  - Clustering can occur due to design (CRT or longitudinal data) or naturally (patients who see the same provider may share unmeasured confounders)
  - Interpretation is conditional
    - e.g., for a given clinic, telehealth palliative care (PC) consults increased completion of an advanced care plan 25% more than in-person PC
  - Best to have at least 10 clusters for robust inference
  - Good option for CRTs or longitudinal data (or when you have both)

Marginal Models

- Generalized estimating equations (GEE)
  - Can only include one random effect
  - Requires a large number of clusters
  - Clustering can occur due to design (CRT or longitudinal data) or naturally (patients who see the same provider may share unmeasured confounders)
  - Marginal interpretation
    - e.g., telehealth palliative care (PC) consults increased completion of an advanced care plan 25% more than in-person PC on average across the study population
  - Not a good option for CRT
  - Good option for longitudinal data

Confounding

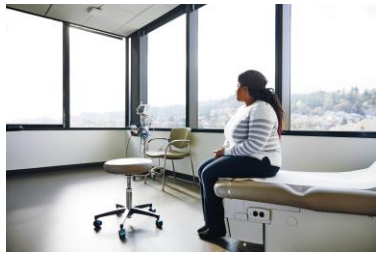
- RCTs should naturally ensure covariates are balanced between treatment arms – simple methods can be used for the analysis (t-test, chi-square)
- CRTs often do not achieve balance – multivariable GLMMs or GEEs that include important confounders are often used
  - Sample size needs to be increased with inclusion of covariates
- Covariate Constrained Randomization of clusters at the design stage can improve covariate balance across clusters
  - Need at least 8 clusters to do CCR

Adjustments

- Design considerations for RCTs and CRTs hold true in studies with hypotheses that include **social determinants of health (SDoH)**
- Randomization may need to be adjusted (stratified block randomization)
- Sample size needs to be increased when interactions are involved

Intervention patients

Control patients



ACCORDS Biostatistics and Analytics Core

- **4** PhD Biostatistician faculty
- **14** MS or PhD-level data analysts
  - Mixed models, longitudinal data analysis, RCT/CRT design, survival, etc.
  - Machine learning, high-dimensional data analysis, public database and EHR data expertise
  - Psychometrics
  - REDCap database development
  - Data Coordinating Center activities
  - Pre-award grant development
- Contact us: https://ucdenverdata.formstack.com/forms/accords_biostats_consult

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Upcoming:
10/16/23: Heather Smyth, CU Anschutz, CIDA (hybrid)
11/20/23: Dustin Rabideau, MGH/Harvard University (hybrid)
12/18/23: Maren Olsen, Duke University (virtual)
01/22/23: Jun Ying, CU Anschutz, DFM (hybrid)
02/26/23: TBD
03/18/23: TBD
04/15/23: Michael Matheny, Vanderbilt University (hybrid)
05/20/23: Keith Goldfeld, NYU (hybrid)