Certificate Program in Practice-Based Research Methods

PBRN Methods: Clustered Designs

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L. Miriam Dickinson, PhD
Professor, University of Colorado School of Medicine
Department of Family Medicine

Donald E. Nease, Jr., MD
Associate Professor
Vice Chair of Research
Director of Community Engagement & Research, Colorado Clinical and Translational Sciences Institute
Director, Shared Networks of Collaborating Ambulatory Practices & Partners (SNOCAP)

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L. Miriam Dickinson, PhD
Donald Nease, MD
University of Colorado

Content

- Background: Review some common research approaches and study designs
- Clustering: a common Features of PBRN research
- Cluster Randomized Trials
- Sample size and power
- Randomization
- Data analysis
- Heterogeneity of treatment effects
- Stepped wedge designs

Background: Review of Some Common Concepts and Study Designs

- **Retrospective**: start with present and look backward at subject's history (e.g. case-control)
- **Cross-sectional**: a snap-shot of subjects at one point in time
- **Prospective**: start with present and follow subjects into the future (cohort study)
  - Retrospective cohort
- Person-time studies – time to event
- Traditional randomized controlled trial (RCT)
- Cluster randomized trial
- Stepped Wedge Trials
- Related concepts:
  - The RE-AIM Framework: Reach, Effectiveness, Adoption, Implementation, Maintenance (Glasgow)
  - Comparative effectiveness and pragmatic trials
  - Implementation and dissemination

Clustering: a common feature of PBRN Research

- Study designs can be observational or experimental
- Retrospective, cross-sectional, or prospective time frames can all be used
- Clustering, or nesting, is a common feature of PBRN research and can apply to any of the common study designs
  - Primary type of PBRN clustering usually involves patients nested within practices (sometimes patients within clinicians within practices)
  - Can include repeated observations on patients over time (longitudinal studies) as well
  - Many studies in PBRNs have both kinds of clustering
- Study design, sampling approaches, power, statistical analysis are *all* affected by clustering

Clustered Randomized Trial (CRT)

- CRTs are a variant of the traditional randomized controlled trial
- Randomized controlled trial is classic experimental study
  - *Patients* are randomly assigned to one of two or more groups (e.g. usual care or intervention) and we observe them to see if the intervention improves outcomes
- In clustered randomized trials in PBRNs the unit of randomization is generally the practice (occasionally some geographic unit, such as communities or counties)
- Some typical reasons for cluster instead of patient level randomization
  - Interventions may target the practice/environment rather than the patient per se
  - Contamination
  - Logistical, cost, and/or ethical concerns
- CONSORT statement: see extension for CRTs
  - http://www.consort-statement.org

Designing a CRT: an example

- Start with your research question
  - Design and analysis should directly address research question and be congruent with the conceptual model
- Example
  - Research questions:
    - Will a practice facilitation approach based on the chronic care model improve patient care and clinical outcomes for diabetic patients
  - Rationale for choice of study design
    - Implementing the intervention within a practice will likely affect all patients, thus contamination would be a serious problem for a traditional RCT
  - CRT hypotheses will be a little different than in a traditional RCT
    - Improvement in quality of diabetes care will be greater for patients in practices receiving the intervention than patients in usual care
    - Improvement in HbA1c will be better for patients in practices receiving the intervention than patients in usual care

Sample Size

- How many practices? How many patients?
  - Involve a biostatistician early in the planning stage and throughout the study
- Power analyses based on number of patients have to be adjusted for clustering
- Intraclass correlation coefficient (ICC) measures the similarity of patients within practices compared to patients in other practices
  - Proportion of the total variance in outcome variable(s) accounted for by clustering – often expressed as a %
- Example: For the primary outcome of HgA1c, previous work indicates that the ICC is about 5%, ICCs for process of care outcomes can be much higher, often as high as 10%

- References : Donner A, Klar N. *Design and Analysis of Cluster Randomization Trials in Health Research*. London, England: Oxford University Press; 2000.
- Dickinson LM, Basu A. Multilevel modeling and practice-based research. Ann Fam Med. 2005 May-Jun;3 Suppl 1:S52-60.

How to determine sample sizes for CRTs

- Determine your primary outcome variables
- Obtain an estimate of the ICC (actual data, literature, this can be challenging, sometimes we just have to guess)
- Calculate the variance inflation factor (VIF): (1 + (m – 1)ICC), where m is the number of patients per practice
- Calculate the effective sample size: divide the proposed sample size (m x number of practices) by the VIF to get the effective sample size
- Do a traditional power analysis

Practices per group	Patients per practice	ICC	VIF	Effective sample size	Effect size	power
6	50	5%	3.45	87	.43	>80%
6	50	10%	5.9	51	.56	80%
6	50	15%	8.35	36	.67	80%
6	100	10%	10.9	55	.55	>80%
10	50	10%	5.9	85	.44	>80%

Randomization

- Now that we know how many practices/patients we need, how do we assign them to groups?
  - Often we recruit just enough practices to do the study
  - Occasionally we have the luxury of sampling practices from a larger pool: stratified sampling may help in this case
- Generally, the number of practices to be randomized is much smaller than trials in which individuals are randomized
- Heterogeneity among practices
- Individuals within practices are more similar to each other than members of other practices
- Simple randomization can result in study arms that are very different from each other, resulting in covariate imbalance between study arms
- Stratified randomization can improve balance but doesn't always solve the imbalance problem
- Minimization methods extended to CRTs

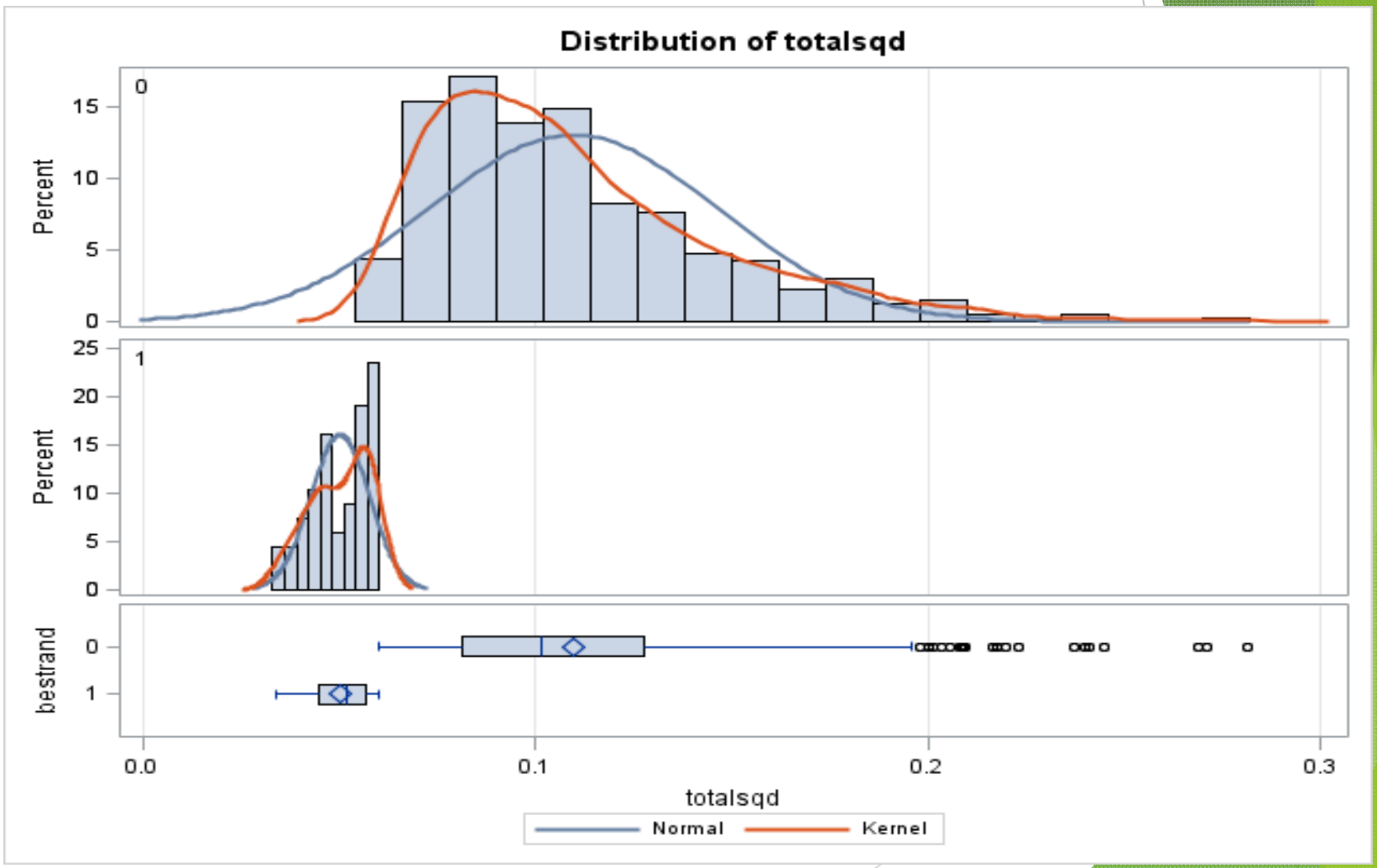
Covariate Constrained Randomization

- Particularly useful for PBRNs is baseline data are available (usually summary data from practices)
- All possible randomizations of units into study groups are generated
- A balance criterion (B), defined as the sum of squared differences between study groups on relevant standardized variables, is calculated for each randomization
  - $B=(w_1(x_{11} - x_{21})^2 + w_2(x_{12} - x_{22})^2 + \ \ldots\ )$
  - Where w is the weight for each selected variable, x11 is the mean for group 1, variable 1, x21 is the mean for group 2, variable 1, etc.
- Establish a criterion for maximum allowable difference between study groups and define a set of "acceptable randomizations" in which the differences between treatment groups on covariates are minimized
- A single randomization is then chosen from the set of "acceptable randomizations"
  - See Dickinson, et al, Pragmatic cluster randomized trials using covariate constrained randomization: A method for practice-based research networks (PBRNs). JABFM. 2015 Sep-Oct;28(5):663-72.

Covariate Constrained Randomization Example: CKD Study Description

- Study objective: To test two approaches to improving care for stage 3 and 4 CKD patients in primary care practices based on the Chronic Care Model (CCM)
- Variables for Randomization aggregated to the practice level
  - Structural and sociodemographic data
    - # FTE clinicians, % African American, % Hispanic, % Medicaid or uninsured
  - Clinical data
    - % of patients with HbA1c>9, % diabetic, % stage 4 CKD, % with systolic BP>130, % with systolic BP>140
    - Mean GFR, mean HbA1c, mean systolic BP
  - Stratification variables handled as part of the procedure by restricting to randomizations with a pre-specified number in each arm by identified strata
  - Achieved balanced study arms (i.e. no significant baseline differences between study arms on aggregated practice level variables)

Distribution of balance criterion



Data Analysis for CRTs

- Describe the sample and address issues of external and internal validity
  - Clustering adds a level to be considered in the CONSORT diagram
    - Describe retention at both the practice and patient level
  - How representative are the patients and practices in this study of the target population? (external validity)
    - Describe practice characteristics
    - Describe patient characteristics
  - Did the randomization work?
    - Compare patients in the intervention group to controls on key variables
    - Variables that differ significantly between groups should be included as covariates in analyses
  - Analytic approaches for clustered data
  - Missingness
  - Did the intervention work?

Did the randomization work?

- Are control and intervention groups similar on key baseline characteristics?
- Compare control and intervention groups on baseline practice and patient characteristics using t-tests and chi-square tests (unadjusted and/or adjusted)
- Example: CRT of two practice facilitation approaches to standard care for improving patient care and clinical outcomes for diabetic patients
  - Stratified randomization approach
  - Practices were similar with regard to rural vs urban location and % Medicaid
  - Patients were similar in terms of sociodemographic characteristics but differed somewhat on clinical variables
  - Baseline process of diabetes care (POC) differed between study arms
    - POC: sum of nine items from the American Diabetes Association Physician Recognition Program: HgA1c, foot exam, blood pressure, dilated eye exam, cholesterol, nephropathy screen, flu shot, nutrition counseling, and self-management support
- See Dickinson WP, et al, Practice Facilitation to Improve Diabetes Care in Primary Care: A Report from the EPIC Randomized Clinical Trial Annals of Family Medicine. 2014; 12(1)8-16.

Longitudinal studies: very important to assess for mechanisms of missingness

- Simplest form of missingness is patient dropout sometime after baseline
  - For dropouts vs completers
    - Compare baseline characteristics using chi-square tests, t-tests, Kendall's tau
    - Compare values of the outcome variable at all observed timepoints
- Key terms
  - MCAR: Missing completely at random – missingness not associated with any observed variables
  - MAR: Missing at random – missingness associated with baseline or subsequent observed variables
  - MNAR: Missing not at random – missingness associated with unobserved characteristics (i.e. patient becomes very ill and drops out)
  - MCAR and MAR are "ignorable" and can be handled analytically using likelihood based models with covariates associated with missingness included
  - MCAR is "non-ignorable" and requires special approaches
- See Fairclough book for more complex situations, including non-ignorable missingness
  - Fairclough DL: Design and analysis of quality of life studies in clinical trials. New York, Chapman & Hall/CRC, 2010

Data Analysis for CRTs

- Some common analytic methods for non-clustered data
  - Simple stats for associations: chi-square tests and t-tests (we use these to compare study groups on baseline data)
  - Multiple logistic (dichotomous outcome) or linear (continuous outcome) with categorical or continuous predictors
  - Survival analysis (e.g. Cox proportional hazards) – outcome is time to event
- Some common analytic approaches for clustered data
  - General (or generalized) linear mixed models (GLMM) (sometimes called mixed effects regression models, multilevel or hierarchical models)
    - Often used to adjust for clustering (e.g. patients within practices) or longitudinal studies with repeated measures on patients, or both
    - GLMMs are a likelihood based approach and can accommodate certain kinds of missing data as well as clustering
  - Generalized estimating equations (GEE)
    - Sometimes used instead of GLMMs, assumptions are different
  - Survival analysis (Cox proportional hazards) - clustered survival analysis can be done

Did the intervention work?

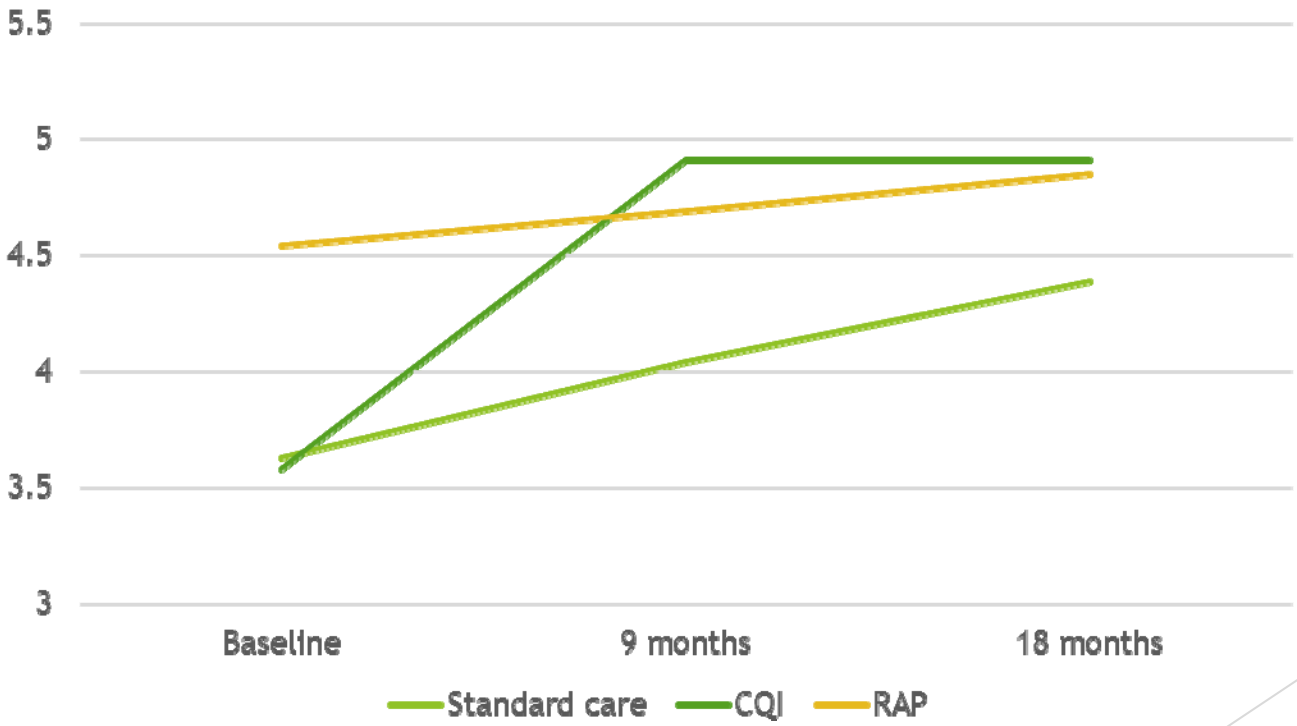
- Since the data are clustered, general linear mixed effects models used for analysis
- Random effect for patient and practice
- Outcome: diabetes POC over time (baseline, 9 months, 18 months)
- Virtually no patient dropout
  - Patient outcomes were obtained retrospectively after the end of the study period on a random sample of patients from each practice using chart review
  - Eligibility criteria included having a visit to the practice sometime during the study period
- Covariate selection is important
  - One approach is to include all covariates associated with the outcome with p-values less than 0.15 to 0.20 in bivariate tests, along with all covariates that are clinically meaningful (e.g. gender), associated with dropout, or differ between groups

Hierarchical and longitudinal model

- Two levels of nesting: Observations are nested within patients (baseline, 9 months, 18 months) and patients are nested within practices
- The intervention effect is actually the time*arm term, which estimates how much patient trajectories over time differ for intervention vs controls
  - Standard care: education and resources only
  - CQI: practice facilitation using continuous quality improvement approach
  - RAP: practice facilitation using a reflective adaptive process
- Basic SAS program is a random intercepts model (it is also possible to include random slopes)

```
PROC MIXED DATA = epic.patient METHOD = ML noclprint covtest;

CLASS practice id arm  time racethnicity  married education comodbidity
insurance;

MODEL  POCdiabetes = female age  racethnicity  married education comorbid
insurance arm  time  time*arm / ddfm=betwithin solution;

random intercept /sub=id(practice) type = un;

random intercept /sub=practice type = un ;

Run;
```

Colorado Epic Study: effectiveness of two approaches to practice facilitation on diabetes process of care



Overall test for differences in trend: p<.001

Moderation and heterogeneity of treatment effects

- Heterogeneity of treatment effects: response to intervention varies by patient or practice characteristics
  - A differential treatment effect involves a baseline moderator variable (sometimes called effect modification)
- In the diabetes study example, contextual effects of practice culture were examined*
- Practice Culture: measured by clinician/staff survey at baseline
  - Change culture (CC): high scores are better
  - Work culture (WC): high scores are better
- We hypothesized that change culture and work culture would *moderate* intervention effectiveness on diabetes POC,
- That is, practices with higher change culture and work culture scores at baseline would respond better (i.e. improve more) to the practice facilitation intervention
- Only two study arms are shown in this example

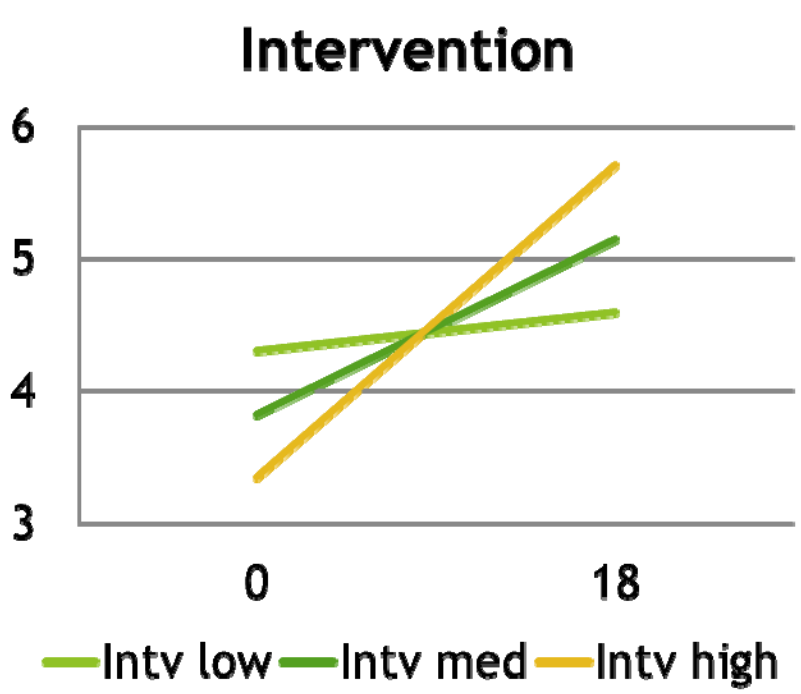
See **Dickinson LM**, et al, Practice context affects efforts to improve diabetes care for primary care patients: A pragmatic cluster randomized trial. Journal of General Internal Medicine. 2015; 30:476-82.

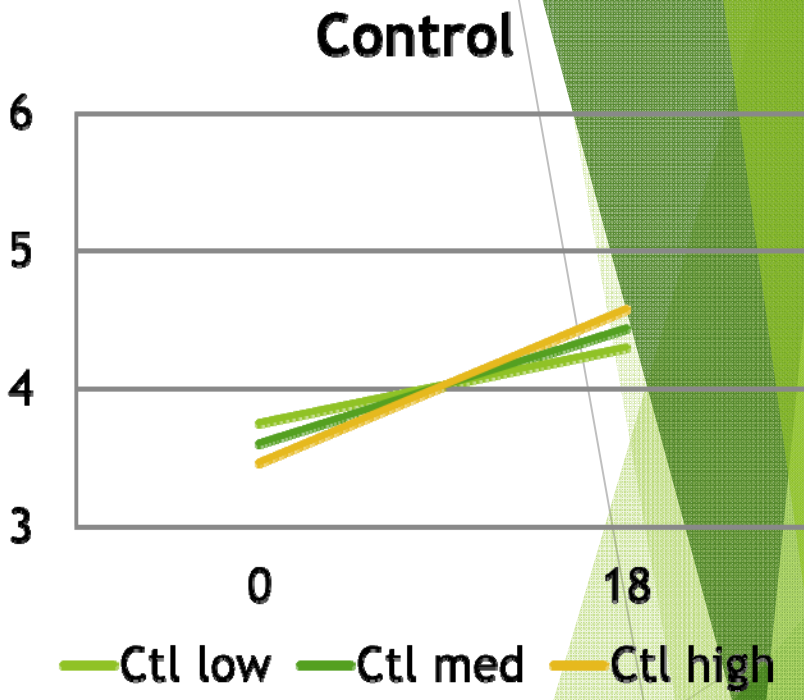
Multilevel model with practice and patient random intercepts

- Basic SAS Code (covariates not shown):
- Moderator analysis for a longitudinal study requires:
  - All main effects of interest (WC, arm, time)
  - All relevant two-way interactions
  - The three-way interaction of interest: differential intervention effect
- SAS code is the same for practice or patient moderator but underlying statistical model is different
- WC is the average practice level score on the Work Culture subscale of the Practice Culture Assessment survey

```
PROC MIXED DATA = epic.patient METHOD = ML noclprint covtest;
CLASS practice id arm   ;
MODEL  POCdiabetes =  arm  time  WC time*arm time*WC arm*WC  arm*WC*time
/ ddfm=betwithin solution;
random intercept /sub=id(practice) type = un;
random intercept /sub=practice type = un ;
Run;
```

Differential intervention effects by practice level baseline work culture scores





- Outcome is diabetes process of care
- Intervention effects differed by work culture: $p<.0001$
- Greater improvement in intervention practices with higher WC scores

Stepped Wedge Designs

- Type of crossover design that's useful when interventions likely to be effective can't be withheld from some practices
  - In practice-based research clusters are generally practices; we use the terms interchangeably here
  - Practices cross over from one condition to another at different times (0=control, 1=intervention)
  - Clusters are randomized to an intervention initiation *order*

Parallel

		Time
		1
Cluster	1	1
	2	1
	3	0
	4	0

Crossover

		Time	
		1	2
Cluster	1	1	0
	2	1	0
	3	0	1
	4	0	1

Stepped Wedge

		Time				
		1	2	3	4	5
Cluster	1	0	1	1	1	1
	2	0	0	1	1	1
	3	0	0	0	1	1
	4	0	0	0	0	1

Hussey & Hughes (2007), *Contemporary Clinical Trials,* Design and analysis of stepped wedge CRT

Stepped Wedge: Randomization and Intervention Initiation

- At the beginning of the trial, all clusters are randomized to an *order* and assigned to a step based on that order
  - In the first time block all clusters are in the control phase
- All clusters (practices) ultimately receive the intervention
  - Randomized intervention initiation order determines *when* (not if) a cluster receives the intervention By the last time block all clusters are in the intervention phase
  - By the last time block all clusters are in the intervention phase
- Traditionally, all *clusters* are recruited and enrolled at baseline and followed for the entire duration of the study (unless retrospective data are available)
- Outcomes measured for every cell (e.g. every time interval for every cluster)

Two Key Design Variations

- Repeated cross-sectional: Clusters cross over but individuals are designated as either control or intervention, depending on point of entry
  - Individuals enrolled during the control phase for that cluster are control subjects
  - Individuals enrolled during the intervention phase for that cluster are intervention subjects
  - Control and intervention groups consist of *different* individuals
- Cohort: Clusters cross over and *individuals change* from control to intervention condition at the time of the cross-over for the cluster
  - The *same individuals* are in the control and intervention phases
  - Individuals, as well as clusters, are followed throughout the entire study period
- Both can occur in the same study

Stepped Wedge Trials: sample size and analytic considerations

- Power analysis for stepped wedge is complex: involve your biostatistician early in planning phase
- Greater power than a parallel group CRT but less than traditional RCT
- Can adjust for temporal trend
- General or generalized linear mixed models can be used for analysis

- References: Hussey & Hughes (2007), *Contemporary Clinical Trials*, Design and analysis of stepped wedge CRT
- Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review (link is external) BMC Med Res Methodol. 2006;6:54.
- AHRQ Stepped Wedge webinar: https://pbrn.ahrq.gov/events/advanced-methods-primary-care-research-stepped-wedge-design

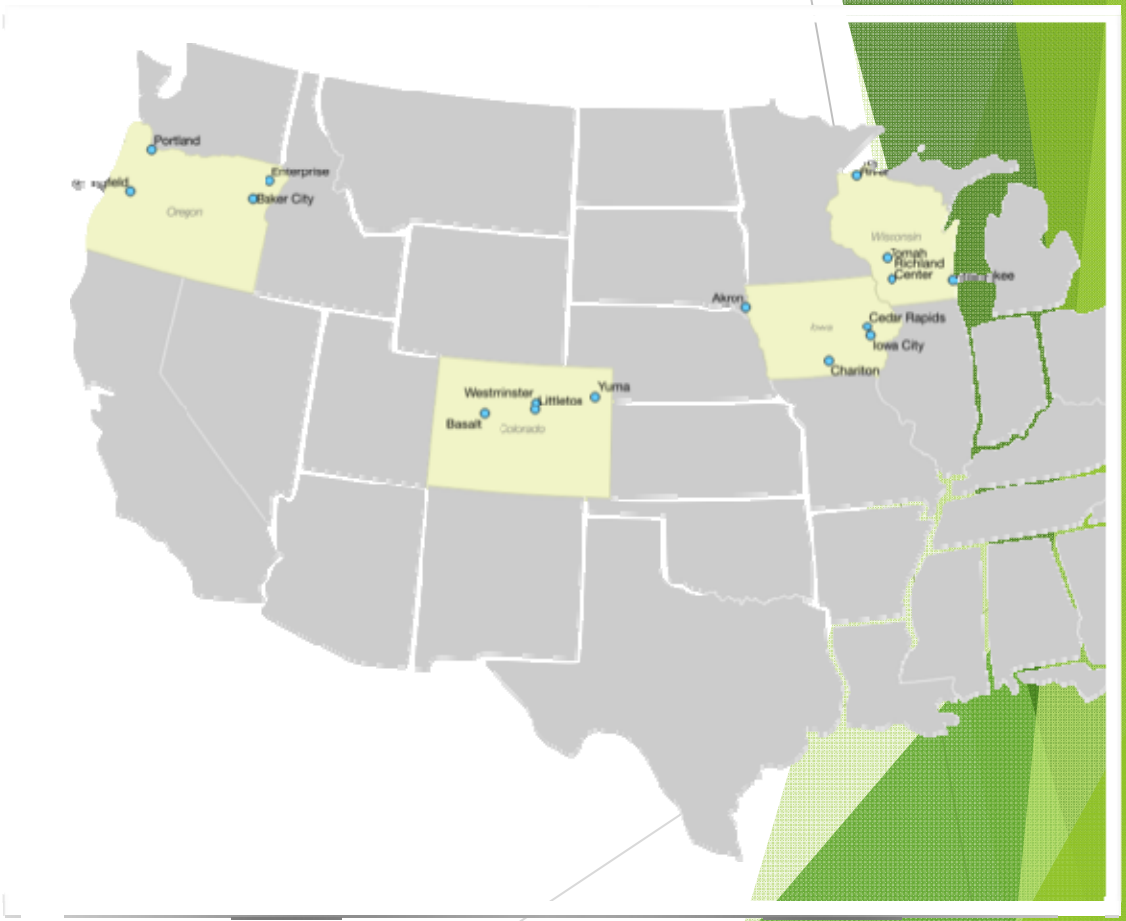
Stepped Wedge Example: Implementing Networks' Self-management Tools Through Engaging Patients and Practices (INSTTEPP)*

- Aims
  - 1. Implement the AHRQ SMS Library/Toolkit across four participating networks and 16 practices using Boot Camp Translation in a stepped-wedge design with 5 time blocks
  - 2. Assess the impact of implementation on practice staff and patients engaged in chronic care management.
  - 3. Identify the factors related to successful implementation

*funded by AHRQ

INSTTEPP

- 4 PBRN's (SNOCAP, ORPRN, WREN & IRENE)
- 16 practices
- 320 patients
- > 80 clinicians and staff



INSTTEPP Study Design

- Repeated cross-sectional for patients: Surveys (Patient Activation Measure & PACIC, self-reported health) at baseline, 1 month, and 2 months after enrollment
  - Patients enrolled during the control phase receive usual care
  - Patients enrolled during the intervention phase receive the intervention (AHRQ SMS Toolkit), with tailored delivery for each PBRN
- Cohort design for practice members: Surveys (CS-PAM & Theory of Planned Behavior) during each of the 5 time blocks
  - Clinicians/staff are in the control condition as long as the practice is in the control phase
  - Clinicians/staff cross over to the intervention phase when the practice crosses over

DM1

Slide 30

DM1 I don't understand this - there were 3 surveys for patients and 5 for clinicians

Dickinson, Miriam, 10/13/2015

Results: Patient Outcomes –
greater improvement in PACIC and self-reported health

	Survey	Control	Intervention	Differential Intervention Effect
Patient Activation Measure	1	66.72	66.07	F(,840)=0.87, p=.3515
	2	66.79	66.72	
	3	66.86	67.36	
Process of Care (from PACIC)	1	31.32	30.19	F(1,791)=16.75, p<.0001
	2	30.76	31.25	
	3	30.20	32.32	
Self-reported health (lower score is better)	1	3.17	3.35	F(1,832)=4.89, p=.0273
	2	3.16	3.25	
	3	3.16	3.16	

Adjusted for age, gender, number of chronic conditions, diabetes, chronic pain

Summary

- Key considerations in choosing a study design
  - Research question
  - Observational or experimental
  - Time frame
  - Budget and resources
  - Logistical and/or ethical concerns
  - Clustered designs
    - Parallel vs stepped wedge
    - Implications for sample size and power
    - Implications for randomization
    - Implications for measurement (especially stepped wedge)
    - Implications for data analysis

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