STEPPED WEDGE DESIGN IN PRACTICE: A CHECKLIST FOR FEASIBILITY

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Outline

- SW design overview
- Checklist for feasibility
- Example: DECIDE-LVAD
- Other challenges

The stepped wedge design

- Quasi-experimental design
  - Hybrid of cluster randomized and cross-over
  - Crossover is unidirectional (C => I)
  - Time of crossover is randomized
- Two versions
  - Cross sectional – enrollment of individuals is continuous, time of enrollment determines treatment assignment
  - Cohort – individuals enrolled at beginning; crossover from C to I occurs within individual

	Time			
1	2	3	4	5
C	I	I	I	I
C	C	I	I	I
C	C	C	I	I
C	C	C	C	I

Reasons for choosing the SW Design

- Evaluate the “effectiveness” or the implementation of an intervention previously shown to be efficacious in an individually randomized trial or in a different setting; systematically evaluate new program
  - **Effectiveness** – all sites participate in the intervention, can continue past end of study
  - **Implementation** – able to study the implementation more carefully as that is spread out over time

Reasons for choosing the SW Design

- **Efficiency**: Units act as their own control (same as cross-over design) => Smaller sample size than cluster randomized design when ICC is large (will define later)
- **Logistical or financial** - cannot introduce the intervention in all units at once; need to study implementation
- **Recruitment of sites** (more willing to participate as all will participate in the intervention)

Statistical Model

Model:

$$Y_{ijk} = \mu + \alpha_i + \beta_j + X_{ij}\theta + e_{ijk}$$

Hussey & Hughes, *Contemp Clin Trials* 2007

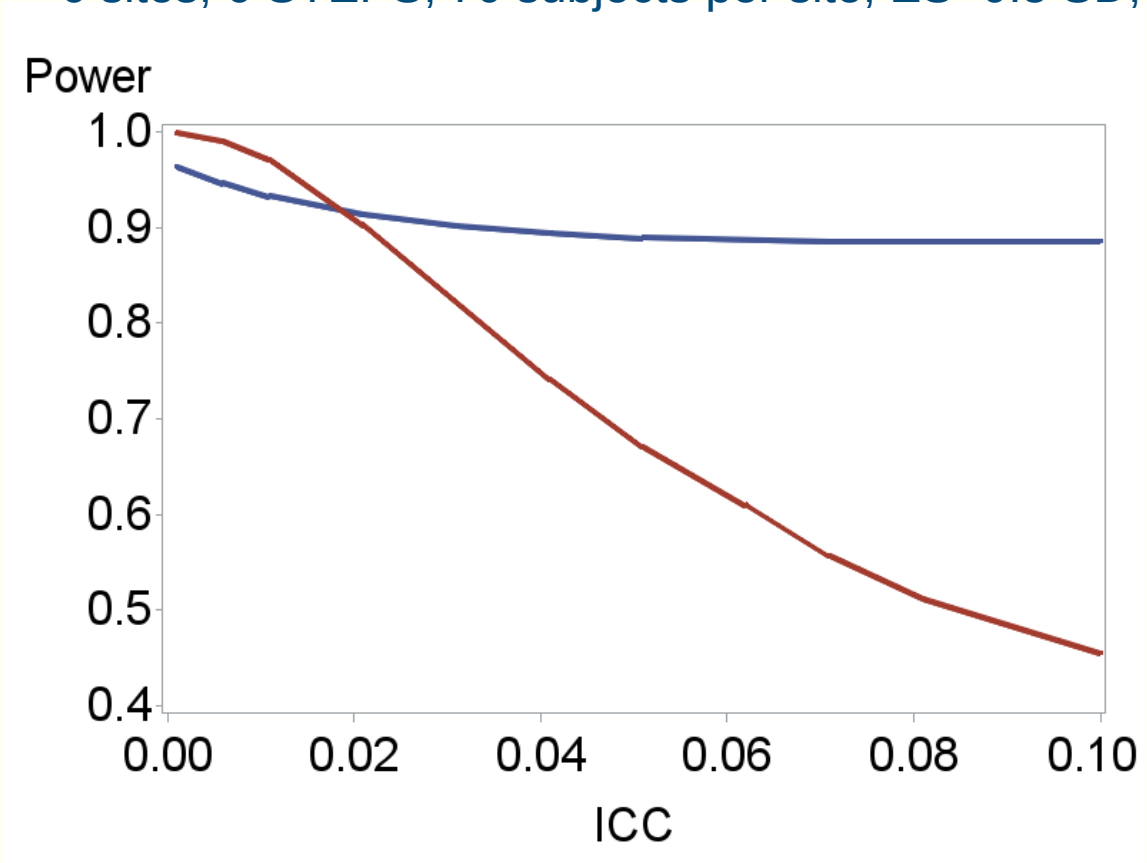
θ	treatment effect
β_j	time effects (constant across cluster)
$\alpha_i \sim N(0,\tau^2)$	between cluster variation
$e_{ijk} \sim N(0,\sigma^2)$	within cluster variation

Key issue determining the power/sample size in a CRT:

$$\text{ICC: } \text{Corr}(Y_{ijk}, Y_{ij'k'}) = \tau^2/(\tau^2 + \sigma^2) \neq 0$$

Power – SW vs CRT

6 sites, 6 STEPS, 70 subjects per site, ES=0.5 SD, alpha=0.05



stepped wedge

cluster randomized

Best thing since sliced bread?

- Why would we not always want to use a SW design vs. a Cluster Randomized Trial?

- Experience with a SW trial (DECIDE) and work on other proposals

Checklist for feasibility

Checklist part 1: Administrative

- ❑ Is it feasible to start enrollment at all the sites at the same time?
  - Coordinating IRBs and subcontracts
  - Hiring of study personnel at each site

- ❑ Are all the sites likely to complete the study (e.g. site dropout is unlikely)
  - Commitment of all sites to complete the study

Part 2: Accrual and Selection Bias

- ❑ Are all sites committed to similar levels of accrual during both control and intervention phases of the trial?
- ❑ Is the pool of potential participants large enough (or continually renewing) to avoid biased selection over time?
  - Very large or renewing pool of participants
  - Steady recruitment that is consistent with respect to patient characteristics (no selection bias)
    - Avoid selection based on visits (sicker patients have more visits)
  - Avoid change in eligible subjects due to intervention

Part 3: Cross-over

- Can the cross-over occur at a specific point in time?
  - Is the **duration of the intervention** short enough to avoid contamination during the cross-over phase of the trial or contamination unlikely?
  - Is the **duration of follow-up** of participants short enough to avoid contamination or is contamination unlikely during follow-up?
  - How much **training** is required? Does the intervention require practice to deliver effectively?

Red Flags/Need for Washout

- Crossover (XO) requires training/practice to implement intervention
- Extended duration of the intervention
  - What do you do with subjects recruited just before the XO
- Follow-up: Potential for contamination of FU after the XO

Washout/Rollout

- Avoiding contamination between the control and intervention phases: extended interventions, extended follow-up
- Training to achieve full effect of intervention

		Time Period						
Treatment sequence	**Site**	**1**	**2**	**3**	**4**	**5**	**6**	
1	**1 Site**	C	WR	I	I	I	I	**Key**
2	**2 Sites**	C	C	WR	I	I	I	C **Control**
3	**2 Sites**	C	C	C	WR	I	I	WR **Washout/Rollout**
4	**1 Site**	C	C	C	C	WR	I	I **Intervention**

N.B. Incomplete designs will dramatically impact the power

Impact of WR on Power

Complete design

	Time						
#	1	2	3	4	5	6	7
1	C	I	I	I	I	I	I
2	C	C	I	I	I	I	I
3	C	C	C	I	I	I	I
4	C	C	C	C	I	I	I
5	C	C	C	C	C	I	I
6	C	C	C	C	C	C	I

Washout/rollout (WR)

	Time							
#	1	2	3	4	5	6	7	8
1	C	WR	I	I	I	I	I	I
2	C	C	WR	I	I	I	I	I
3	C	C	C	WR	I	I	I	I
4	C	C	C	C	WR	I	I	I
5	C	C	C	C	C	WR	I	I
6	C	C	C	C	C	C	WR	I

Scenario	Total N	C or I N/cell	WR N/cell	*Power
Complete	840	20	NA	0.80
WR	840	20	0	0.66
WR	1176	28	0	0.79

*6 sites, 7\8 time periods (complete\WR), alpha=0.05, ICC=0.1

Part 4: External/Internal Time Trends

- Is it unlikely that events or changes in policy might result in time trends that occur in some sites but not all sites?
  - Maybe alternative analytic models, but should be pre-specified. Cutting edge with respect to analysis (e.g. evolving literature).

Example: DECIDE-LVAD

- Drs Larry Allen and Dan Matlock, UC-SOM
- **Population** – Patients with heart failure considering LVAD implantation (and caregivers)
- **Intervention** – Decision aid
- **Goals:** Study Effectiveness and Implementation
- **Outcomes**
  - LVAD knowledge (~1 week FU),
  - Values-treatment concordance (1 month FU)
- **SW details** – 6 LVAD centers across the US (CU required to start first)

Example: DECIDE

	Enrollment/Time Period					Total	
Site	1	2	3	4	5	Cntrl	Invtn
1	13	8	12	7	1	13	28
2	5	6	4	3	4	11	11
3	4	9	16	15	11	13	42
4	10	7	8	7	4	25	11
5	8	8	12	5	2	28	7
6	18	11	6	10	14	45	14
Total	58	49	58	47	36	135 (54%)	113 (46%)
Outpatient (%)	16%	14%	29%	30%	31%	17%	31%
HF Dx > 4 yrs (%)	82%	84%	65%	75%	68%	77%	64%

DECIDE: Checklist Administrative

- ❑ Is it feasible to start enrollment at all the sites at the same time?
  - One site started late (only by one month) – due to IRB/subcontract administrative approval process

- ❑ Are all the sites likely to complete the study (e.g. site dropout is unlikely)
  - One site stopped enrollment for a short time during the middle of the study period

Ref: Matlock et al

DECIDE: Checklist Accrual

- ❑ Are all sites committed to similar levels of accrual during both control and intervention phases of the trial?
  - Accrual declined in most sites over time, except one site
  - Control: N=135, Intervention: N=113
  - Original Target: 65 per arm.
- ❑ Is the pool of potential participants large enough (or continually renewing) to avoid biased selection over time?
  - Proportion of Outpatients increased over time
    → 17% in Control; 31% in Intervention
  - Proportion with Initial DX >4 years decreased over time
    → 77% in Control; 64% in Intervention

DECIDE: Checklist Cross-over

- ❑ Can the cross-over occur at a specific point in time?
  - ❑ Is the **duration of the intervention** short enough to avoid contamination during the cross-over phase of the trial or contamination unlikely?
    - Short duration of intervention for participants – viewing of pamphlet and video
  - ❑ Is the **duration of follow-up** of participants short enough to avoid contamination or is contamination unlikely during follow-up?
    - Contamination unlikely during follow-up – outcomes measured at ~1 week and 1 month
  - ❑ How much **training** is required? Does the intervention require practice to deliver effectively?
    - Site training: study staff visited each site right before cross-over. No practice needed, but changes such that pamphlet and video are offered

DECIDE: Checklist Time Trends

- ❑ Is it unlikely that events or changes in policy might result in time trends that occur in some sites but not all sites?
  - This was considered unlikely – potential events (celebrity implantation of LVAD, standard of care/treatment/industry materials) were considered to be likely to change things across all sites, if they occurred

Other Challenges

- Sample size calculations:
  - Not difficult if all the sites are the same size and can recruit the same number of participants during each period
  - More challenging if
    - site sizes are variable,
    - accrual over time is variable,
    - washout is needed at crossover
    - other non-standard SW design or hybrid

Other Challenges (2)

- Randomization
  - Balancing sites by size
    - Identifying large and small sites
  - Balancing site level covariates
  - Balancing participant level covariates

Other Challenges (3)

- Analysis methods
  - Hussey and Hughes model is straight forward and quite robust if confounding covariates are measured and included in the model, but may not address all concerns
  - Varying time effects by cluster or groups of clusters
    - See Hooper et al (2016), Hemming et al (2017)
  - Varying treatment effect by cluster or groups of clusters
    - See Hemming et al (2017), Thompson et al (2017)
  - Treatment effect varying over time
    - See Hemming et al (2017)
  - Other robust methods:
    - Ji et al (2017), Wang & De Gruttola (2017), Thompson et al (2018), Hughes et al (2019)

Summary – To SW or Not?

- Checklist
- Strong statistical support
- Other discussions
  - deHoop (2015) BMC Med Res Method
  - Hargreaves (2015) Trials
  - Hemming (2015) BMJ
  - Taljaard (2016) Clinical Trials
  - Eichner (2019) JCE

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