DECIDE-LVAD Trial – Stepped Wedge Design

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Associate Professor of Medicine
University of Colorado School of Medicine
Implementation Scientist - GRECC
Shared Decision Making

informed consent
Shared Decision Making

“A meeting between experts”

Paternalism

Consumerism (abandonment)

Tuckett, 1985
Design and Testing of Tools for Shared Decision Making

Daniel D. Matlock, MD, MPH; Erica S. Spatz, MD, MHS

Step 1: Needs Assessment/Content Development
- Patient, caregiver, clinician interviews
- Clinician/Technical advisory panel
- Evidence review

Step 2: Draft paper version

Step 3: Iterative Development
Patient and clinician review
- Accurate
- Understandable
- Unbiased

Step 4: Paper version 1

Step 5: Video script draft

Step 6: Iterative Development
Patient and clinician review
- Accurate
- Understandable
- Unbiased

Step 7: Filming

Step 8: Initial Video Prototype

Step 9: Patient and expert review

Step 10: Technical expert panel considers patient and expert recommendations, final edits

Final paper and video decision aids
Decision Aid: Paper Tools

Path 1
You may choose to get an ICD. You may be feeling like you usually do, then a dangerous heart rhythm could happen. The ICD may help you live longer by treating a dangerous heart rhythm. You will continue to live with heart failure that may get worse over time.

Feel Healthy
Feel Sicker
Death
Last years of life

"I'm not ready to die. I have so much I'm trying to stay alive for. Even if it means getting shocked, I'm willing to do anything that can help me live longer."

Path 2
You may choose to NOT get an ICD. You may be feeling like you usually do and then a dangerous heart rhythm could happen. You may die quickly from the dangerous heart rhythm.

Feel Healthy
Feel Sicker
Death
Last years of life

"I've lived a good life. The idea of dying quickly sounds like a painless way to go. I've always said I hope to die in my sleep. Going through surgery and getting shocked is not the kind of thing I want."

With an ICD
29 die, 71 live
Without an ICD
36 die, 64 live

Number of people who live because of the ICD
Number of people who die
Number of people not affected

www.patientdecisionaid.org
Decision Aids – Do They Work?

• Cochrane Review of 115 trials of Decision aids
  • Improved knowledge
  • Improved value/treatment concordance
  • Improved patient/doctor communication
  • Improved patient involvement
  • Improved Satisfaction
  • Lowered decision conflict
  • Lowered decision regret
  • Lowered the proportion undecided

Stacey D, Cochrane Review, 2014
Implementation is hard!

• Who will deliver the Decision aid?
  • Provider?
  • Staff member
    • empowered to provide DA on behalf of provider

• How will the DA be delivered?
  • Electronically
    • With EHR? Patient portal? Email?
  • In person or mailed
    • Print, DVD?
Implementation is hard!

• Medical decisions require different depths of deliberation
  • Daily, reversible vs. single, irreversible decisions

• When will the DA be delivered?
  • Timing important for shared decision making
    • Before visit may set up SDM
    • In visit can directly support SDM interactions
Clinicians lacked confidence in the content of the DAs
- Many concerns about DAs disrupting established workflows
- Lack of incentives a major barrier
Left Ventricular Assist Device (LVAD) for Destination Therapy
A device for patients with advanced heart failure

Exploring Options

www.patientdecisionaid.org
The Artificial Heart is For Real

Barney Clark
1982

Dick Cheney
2010
LVAD Growth
A Multicenter Trial of a Shared Decision Support Intervention for Patients and their Caregivers Offered Destination Therapy for End-Stage Heart Failure

Principal Investigator
Larry A. Allen, MD, MS

Organization
University of Colorado Denver

State
Colorado

Year Awarded
2014

Funding Announcement
Communication and Dissemination Research

Project Budget
$2,052,964

Project Period
3 Years
**Objective**

Understand the effectiveness and implementation of a shared decision support intervention for advanced heart failure patients considering DT LVAD.
Study Designs for DECIDE-LVAD Trial

• **Classic patient-level** randomization
  • Intervention is patient AND program-based; not at individual-level
  • Diffusion among participants at each site is probable

• **Cluster** randomization
  • Concerns about statistical power with only 6 total sites
    • 3 sites intervention, 3 sites control
    • Homogeneity of intervention participants and control participants

• **Stepped wedge cluster randomization** . . .
DECADE-LVAD Trial

**Figure 5.** Stepped wedge randomization scheme.

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<tr>
<th>Site</th>
<th>Pre 4 months</th>
<th>Phase 1 4 months</th>
<th>Phase 2 4 months</th>
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- **Control Period**
- **Roll-Out**
- **Intervention Period**
Evaluation Framework

• **Reach:**
  • % eligible patients and caregivers

• **Effectiveness**
  • Increased knowledge
  • Value-treatment concordance

• **Adoption**
  • Taken up by key personnel

• **Implementation**
  • Consistently used

• **Maintenance**
  • Continued use after trial completion
Implementation Intervention

- **Pre-implementation:**
  - Planning, identifying key people

- **Implementation visit**
  - 1 hour: Grand rounds presentation (large audience)
  - 1 hour: Communication Training (heart failure team)
  - 1 hour: Discuss new process
    - Already a delivery process “plug and play”

- **Post-implementation**
  - Ongoing site support
  - Follow-up visit
Primary Outcome: DECISION QUALITY

“The extent to which medical decision making reflects the considered preferences of a well-informed patient.”

Values-Choice Concordance

Higher-Quality LVAD Decision

Option chosen optimizes values, goals, and preferences

An informed patient

Primary Outcome: DECISION QUALITY

Lower-Quality LVAD Decision

Knowledge
Values-Choice Concordance

Values

LVAD

Do everything I can to live longer, even if that means having major surgery and being dependent on a machine.

Concordant

Choice

LVAD

No LVAD

Live with whatever time I have left, without going through major surgery or being dependent on a machine.
Values-Choice Concordance

**Values**
- Do everything I can to live longer, even if that means having major surgery and being dependent on a machine.

**Choice**
- LVAD
- No LVAD

**Discordant**

- Live with whatever time I have left, without going through major surgery or being dependent on a machine.
Participants

248 patients enrolled (from n=385 eligible; power/planned n=168)

- Enrolled patients more likely to be white non-Hispanic than non-enrolled (75% vs. 64%)

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<th>Control (n=135)</th>
<th>Intervention (n=113)</th>
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<td>Age, mean years (SD)</td>
<td>63.5 (9.7)</td>
<td>63.2 (10.2)</td>
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<td>Male</td>
<td>82.2%</td>
<td>86.7%</td>
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<td>White, non-Hispanic</td>
<td>79.1%</td>
<td>82.7%</td>
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<td>Some college or more</td>
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<td>On Disability</td>
<td>27.6%</td>
<td>32.0%</td>
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<td>Married</td>
<td>72.5%</td>
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<td>Diagnosed &lt; 2 years</td>
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<td>Enrolled in ICU</td>
<td>21.5%</td>
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<td>INTERMACS 4-7 (p&lt;0.01)</td>
<td>18.3%</td>
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Intervention Delivery

- Training
  - All sites participated: 31-72 staff per site

- Patient decision aid exposure
  - 88% received pamphlet decision aid
  - 92% received video decision aid

- “Educational materials” felt to be biased in favor of LVAD
  - 54% of control patients
  - 43% of intervention patients (p=0.13)
Knowledge

- Control: 59.5% → 64.9%
- Intervention: 59.1% → 70.0%
- Adjusted difference of difference: **5.5%**
Values-Choice Concordance

- Control: 0.17 correlation coefficient
- Intervention: 0.48 correlation coefficient
- Adjusted difference of difference: 0.28

Higher-Quality LVAD Decision

Lower-Quality LVAD Decision

Percent difference, mean (baseline 1 to baseline 2)
Secondary Outcomes: 6-month implant

Adjusted for Site and Time Period

P=0.008

26% decrease in patient going on to LVAD
Thank You

- Core Team:
  - Bryan Wallace
  - Jocelyn Thompson
  - Channing Tate
  - Colleen McIlvennan
  - Carmen Lewis
  - Jean Kutner
  - Russ Glasgow
  - Amy Jenkins
  - Pilar Ingle
  - Gracie Finnigan-Fox
  - Diane Fairclough
  - Erin Chaussee
  - Larry Allen

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WWW.PATIENTDECISIONAID.ORG
Stepped Wedge Cluster Randomized Trials

Diane L Fairclough, DrPH
Erin Leister Chaussee, MS

Pragmatic Research Conference
June 5, 2019
The stepped wedge design

• Quasi-experimental design
  • Hybrid of cluster randomized and cross-over
  • Crossover is unidirectional (O => X)
  • Time of crossover is randomized

• Two versions
  • Cross sectional – enrollment of individuals is continuous, time of enrollment determines treatment
  • Cohort – individuals enrolled at beginning; crossover from O to X occurs within individual

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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, so fewer units needed (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)
Statistical Model

Model:

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

- \( \theta \): treatment effect
- \( \beta_j \): 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:

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

Hussey & Hughes, *Contemp Clin Trials* 2007
Power – SW vs CRT

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

Power

stepped wedge

cluster randomized

ICC
Key Considerations

• What is the primary aim of the study?
  • Demonstration of efficacy
  • Demonstration of effectiveness in practice
  • Assessment of implementation
• What is the unit of randomization?
  • Individual
  • Practice, Clinic, Region
• How/to whom is the intervention delivered?
• How/on whom is the outcome measured?
Example: DECIDE

• Primary aim of the study?
  • Effectiveness and Implementation

• Unit of randomization?
  • Clinic/Site

• How/to whom is the intervention delivered?
  • Patient/single encounter

• How/on whom is the outcome measured?
  • Patient/Caregiver
    • Interview/Questionnaire: Pre and Post (1 week, 1 month, 6 months)
    • Contamination of Control unlikely after transition to Intervention
Challenges - Administrative

• Starting and Ending Accrual and Follow-up at the same time in all sites
  • Coordinating IRBs and subcontracts
  • Commitment of all sites to complete the study
• Steady recruitment that is consistent with respect to patient characteristics (no selection bias)
  • Very large or renewing pool of participants
  • Avoid selection based on visits (sicker patients have more visits)
  • Change in eligible subjects due to intervention
• Limiting to settings where site specific temporal changes are unlikely
## Example: DECIDE

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<td>Total</td>
<td>58</td>
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<td>47</td>
<td>36</td>
<td>135 (54%)</td>
<td>113 (46%)</td>
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</table>

| Outpatient | 16% | 14% | 29% | 30% | 31% | 17% | 31% |
| Dx > 4 yrs (%) | 82% | 84% | 65% | 75% | 68% | 77% | 64% |
Challenges

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

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<th>Treatment sequence</th>
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N.B. Incomplete designs will dramatically impact the power
Analysis Models

• GLMM
  • Unit of obs = Individual
  • Distributions – Normal, Binomial, Poisson, Cox
  • Hussey and Hughes
  • $f(Y_{ijk}) = \mu + \alpha_i + \beta_j + X_{ij}\theta + \epsilon_{ijk}$
  • Variations (Hemming (2017) Trials:
    • Add covariates
    • Repeated measures within individual
    • Treatment effect varies with time since intervention started
    • Cluster x Time, Cluster x Treatment, Treatment x Time
    • Fixed effects for clusters => GLM
Analysis Models

• Linear Mixed Model
  • Unit of obs=Summary Data for each cluster at each time period

• GEE models
  • Outcome generally binomial
  • Specify the working covariance structure (e.g. exchangeable)
Summary – To SW or Not?

• Recent discussions
  • Hargreaves (2015) Trials
  • Hemming (2015) BMJ
  • Taljaard (2016) Clinical Trials
  • Fairclough (????)
Checklist: Feasibility of SW Design (1)

- Is it feasible to start enrollment at all the sites at the same time?
- Are all the sites likely to complete the study (e.g. site dropout is unlikely)?
- 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?
Is the duration of the intervention short enough to avoid contamination during the cross-over phase of the trial or is it feasible to insert a wash-out periods between the control and the intervention phases?

Is the duration of follow-up of participants short enough to avoid contamination or is contamination unlikely during follow-up?

Are there events or changes in policy that might result in time trends that are likely to occur in some sites but not all sites?
Stepped Wedge
Power and Sample Size
SW Power

- Depends on …
  - strength of treatment effect
  - number of clusters (more better, balanced by logistics)
  - number of steps, **number of clusters per step**
  - number participants per cluster per step
  - variance components: $\sigma^2$ (easy to know), $\tau^2$ (hard to know)
  - design variations, ex: **incomplete designs**
  - variability of cluster sizes and enrollment numbers over time
SW Power

• SW vs CRT
  • SW more efficient (fewer clusters, fewer total participants) than CRT at larger ICCs

• Risks for studies with small number of clusters
  • Taljaard (2016) Clinical trials
    • Limited generalizability, limited options for analysis
    • Increased sensitivity of power calculations to the assumptions
    • Increased risk of Type I and Type II error
  • Barker (2017) Trials
    • Recommendations for minimum number of SW clusters for fixed number of time periods – Type I errors, model fit and convergence

• Other thoughts
  • Increased sensitivity to performance of an individual site
  • Increased sensitivity to unmeasured confounders (vs indiv rand)
**SW Power**

Optimal SW power: each cluster rolls over at its own time period (HH)

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For a fixed number of time periods, optimal power when max number of clusters are first and last to transition (Lawrie et al)

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SW Power

Designs with a transition/washout period: depending on number of unique treatment sequences, can have substantially less power than a standard “complete” SW design

Hybrid designs – could get additional power if able to “nest” a SW within a CRT (Thompson et al)
# SW Power: Incomplete Designs

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<th>Scenario</th>
<th>Total N</th>
<th>O or X N/cell</th>
<th>WR N/cell</th>
<th>*Power</th>
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<td>20</td>
<td>NA</td>
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<td>Incomplete</td>
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<td>28</td>
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<td>0.79</td>
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*6 sites, 6 steps, alpha=0.05, ICC=0.1
# SW Power/Sample Size Tools

<table>
<thead>
<tr>
<th>Application</th>
<th>Notes</th>
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</table>
| R: swCRTdesign | **Hughes J** [http://faculty.washington.edu/jphughes/pubs.html](http://faculty.washington.edu/jphughes/pubs.html)  
  - SW design, including variants such as fractional treatment indicator and incomplete designs |
| R: SWSamp | **Baio et al. Trials 2015**  
  - Both HH and simulation based power methods  
  - Flexible in terms of outcome distribution |
| R-Shiny: https://clusterrcts.shinyapps.io/rshinyapp/ | **Hemming K, Kasza J, with input from Hughes J**  
  - CRT, SW, SW design variants, inflation factor for variable cluster sizes |
| Stata: steppedwedge | **Hemming & Girling. Stata J 2014**  
  - CRT, SW, some of the SW design variants |
| PASS (version 15+) |  
  - Tests of two proportions, means, or Poisson rates |
References

1) Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemporary Clinical Trials 2007
2) Hemming et al. The stepped wedge cluster randomized trial: rationale, design, analysis, and reporting. BMJ 2015
3) Taljaard et al. Substantial risks associated with few clusters in cluster randomized and stepped wedge designs. Clinical Trials 2016
5) Barker et al. Minimum number of clusters and comparison of analysis methods for cross sectional stepped wedge cluster randomized trials with binary outcomes: a simulation study. Trials 2017
6) De Hoop et al. The need to balance merits and limitations from different disciplines when considering the stepped wedge cluster randomized trial design. BMC Med Res Method 2015.
10) Thompson et al. The optimal design of stepped wedge trials with equal allocation to sequences and a comparison to other trial designs. Clinical Trials 2016.