DECIDE-LVAD Trial – Stepped Wedge Design

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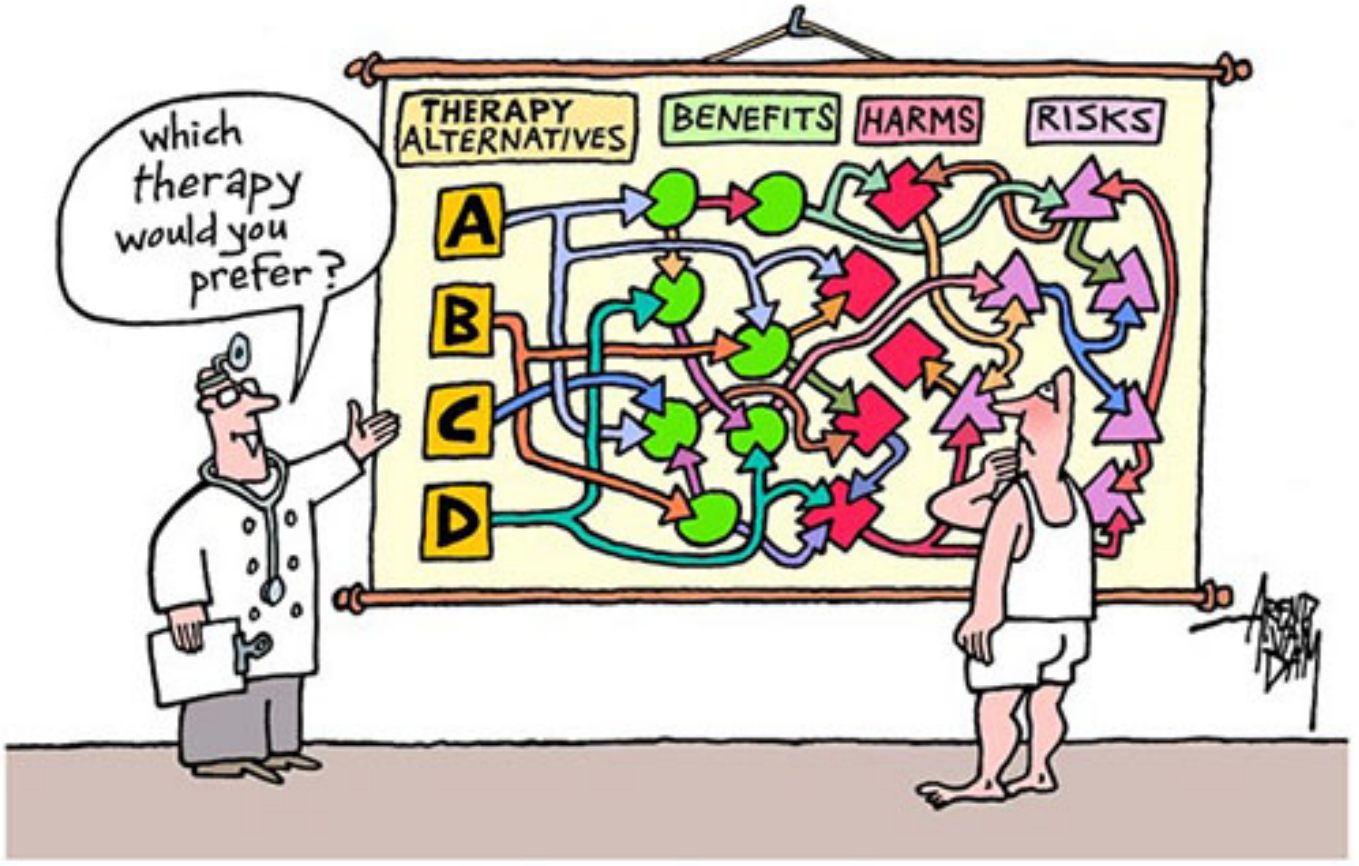
Implementation Scientist - GRECC

Shared Decision Making



informed consent

Shared Decision Making

"A meeting between experts"

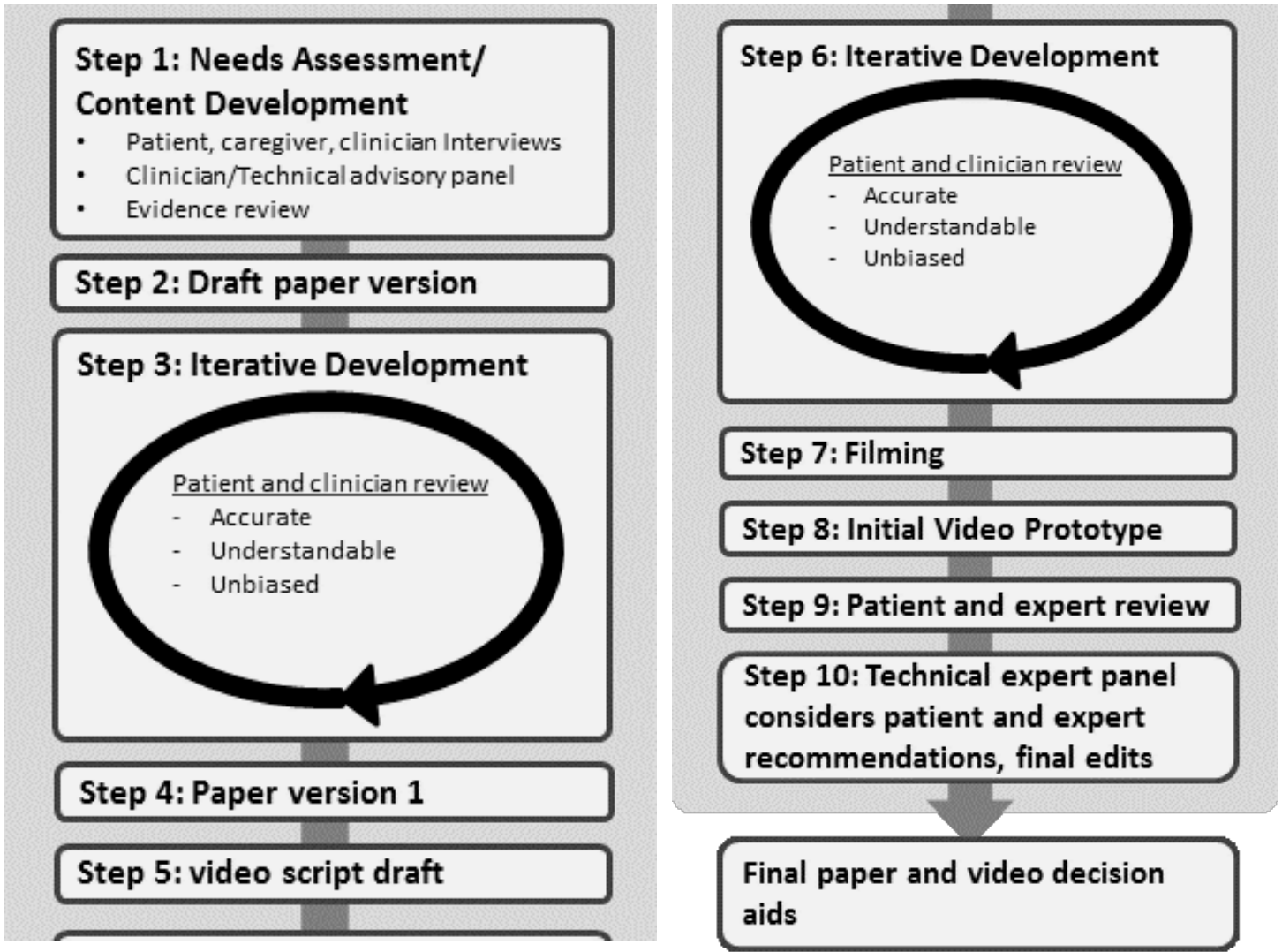
Tuckett , 1985

Paternalism

Consumerism (abandonment)

Design and Testing of Tools for Shared Decision Making

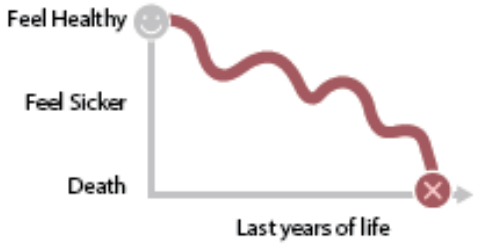
Daniel D. Matlock, MD, MPH; Erica S. Spatz, MD, MHS



Decision Aid: Paper Tools

Path 1

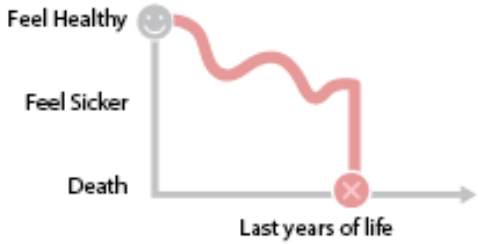
You may choose to get an ICD. You may be feeling like you usually do, then a dangerous heart rhythm could happen. The ICD may help you live longer by treating a dangerous heart rhythm. You will continue to live with heart failure that may get worse over time.



"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.



"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."

www.patientdecisionaid.org

Decision Aid Tools: Video

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!

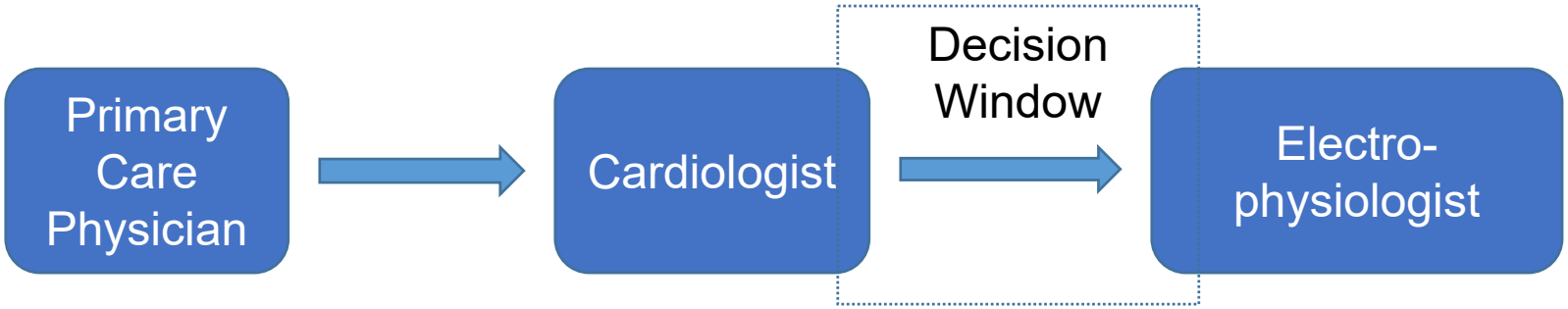
- Who will deliver the Decision aid?
  - Provider?
  - Staff member
    - empowered to provide DA on behalf of provider

- 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

- <u>When will the DA be delivered?</u>
  - Timing important for shared decision making
    - Before visit may set up SDM
    - In visit can directly support SDM interactions



Elwyn *et al. BMC Medical Informatics and Decision Making* 2013, **13**(Suppl 2):S14
http://www.biomedcentral.com/1472-6947/13/S2/S14

BMC
Medical Informatics & Decision Making

REVIEW **Open Access**

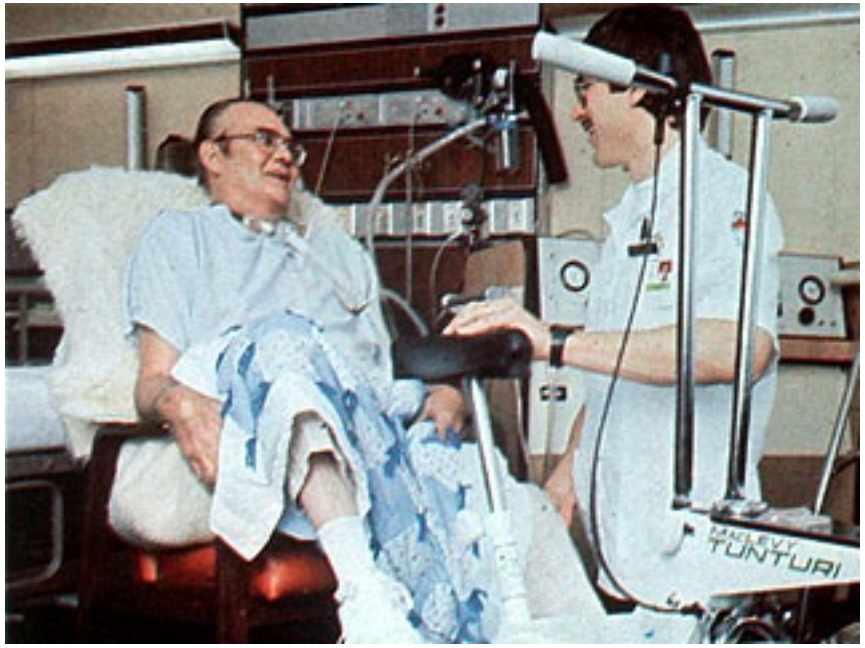
"Many miles to go …": a systematic review of the implementation of patient decision support interventions into routine clinical practice

- Clinicians lacked confidence in the content of the DAs
- Many concerns about DAs disrupting established workflows
- Lack of incentives a major barrier

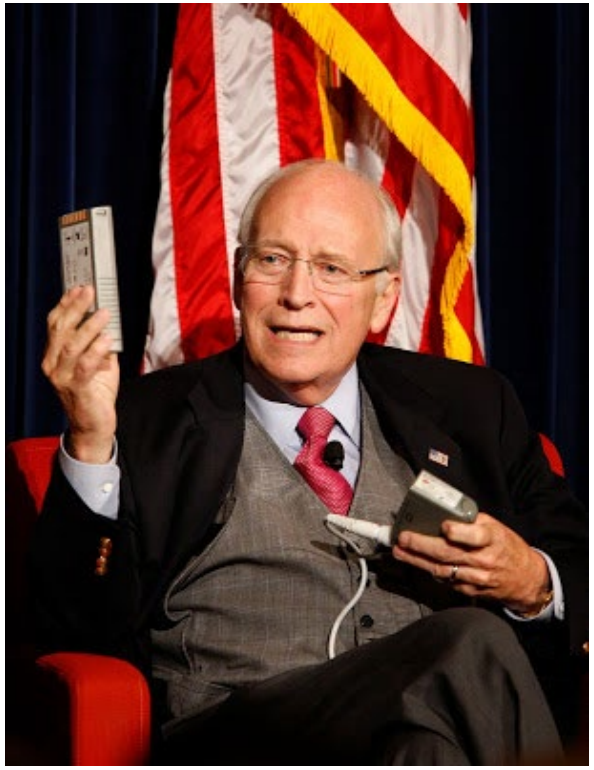
Left Ventricular Assist Device (LVAD) for Destination Therapy

A device for patients with advanced heart failure

The Artificial Heart is For Real

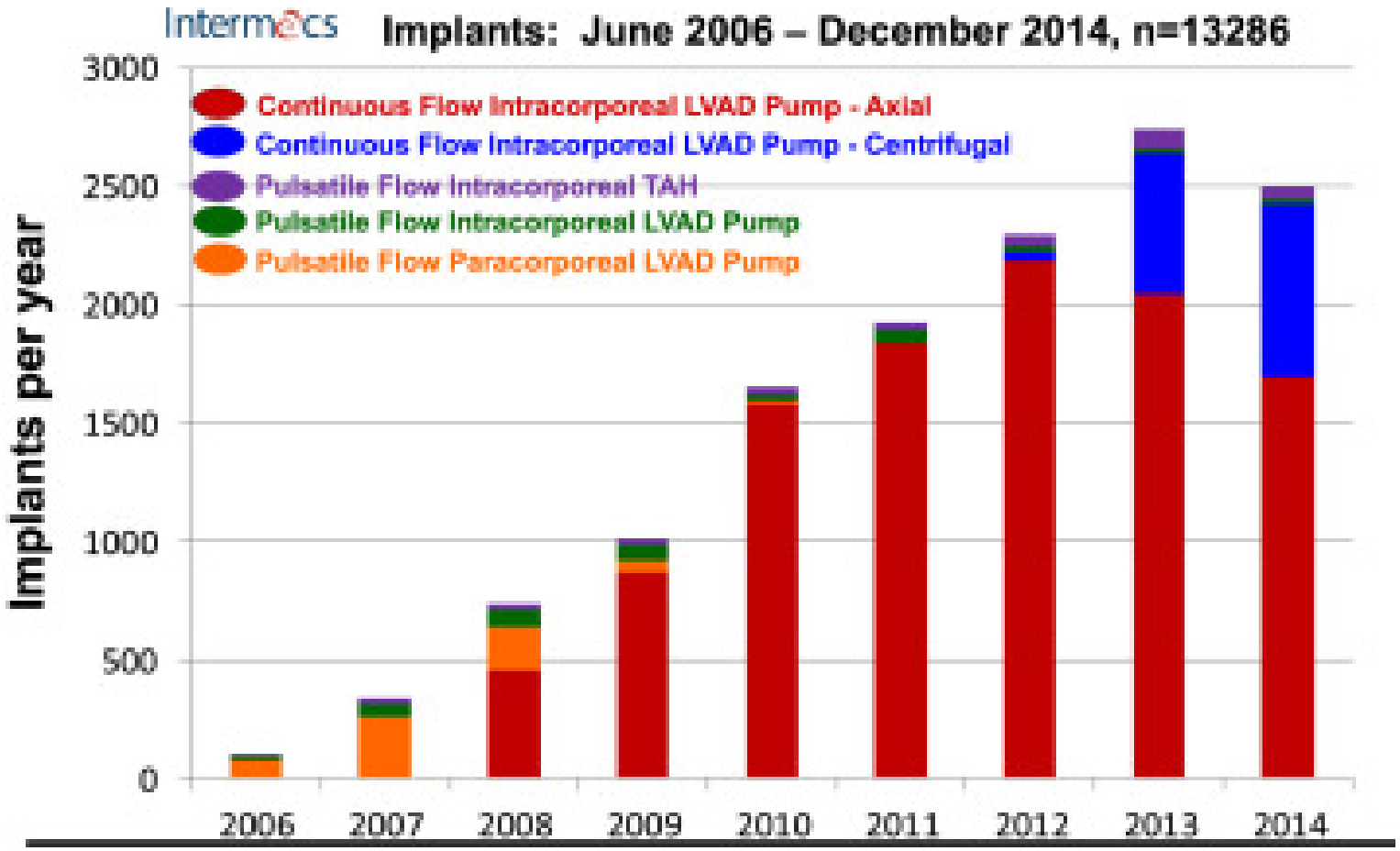


Barney Clark
1982



Dick Cheney
2010

LVAD Growth


Intermacs
Implants: June 2006 – December 2014, n=13286
Implants per year
3000
2500
2000
1500
1000
500
0
Continuous Flow Intracorporeal LVAD Pump - Axial
Continuous Flow Intracorporeal LVAD Pump - Centrifugal
Pulsatile Flow Intracorporeal TAH
Pulsatile Flow Intracorporeal LVAD Pump
Pulsatile Flow Paracorporeal LVAD Pump
2006
2007
2008
2009
2010
2011
2012
2013
2014

DECIDE – LVAD trial

pcori Patient-Centered Outcomes Research Institute

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Search

ABOUT US FUNDING OPPORTUNITIES RESEARCH & RESULTS GET INVOLVED MEETINGS & EVENTS

Research & Results

OUR PROGRAMS

RESEARCH WE SUPPORT

HOW WE SELECT RESEARCH TOPICS

RESEARCH METHODOLOGY

PCORNET: THE NATIONAL PATIENT-CENTERED CLINICAL RESEARCH NETWORK

RESEARCH IN ACTION

COLLABORATING WITH OTHER

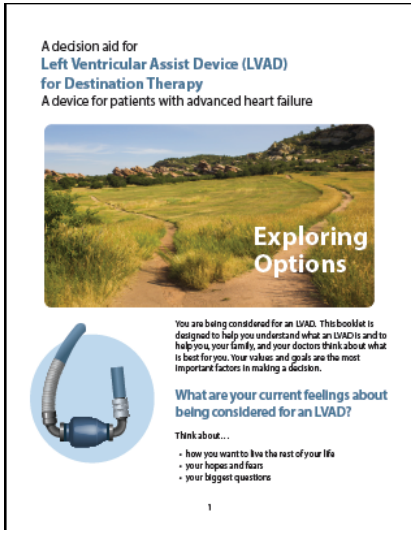
A Multicenter Trial of a Shared Decision Support Intervention for Patients and their Caregivers Offered Destination Therapy for End-Stage Heart Failure

Principal Investigator
Larry A. Allen, MD, MS

Organization	Funding Announcement
University of Colorado Denver	Communication and Dissemination Research
State	**Project Budget**
Colorado	$2,052,964
Year Awarded	**Project Period**
2014	3 Years

DECIDE-LVAD Trial

Objective: Understand the effectiveness and implementation of a shared decision support intervention for advanced heart failure patients considering DT LVAD.


A decision aid for
Left Ventricular Assist Device (LVAD)
for Destination Therapy
A device for patients with advanced heart failure

Exploring Options

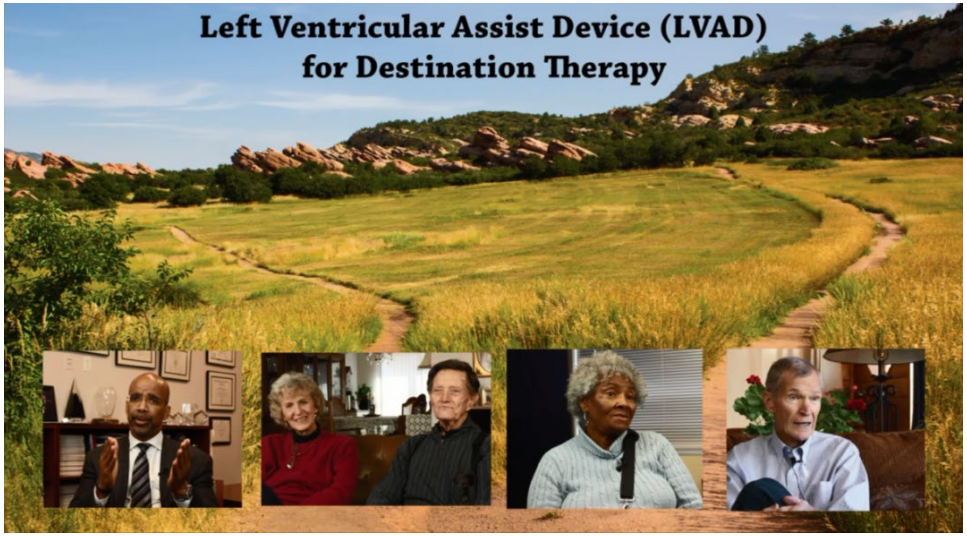
You are being considered for an LVAD. This booklet is designed to help you understand what an LVAD is and to help you, your family, and your doctors think about what is best for you. Your values and goals are the most important factors in making a decision.

What are your current feelings about being considered for an LVAD?

Think about…

- how you want to live the rest of your life
- your hopes and fears
- your biggest questions

1

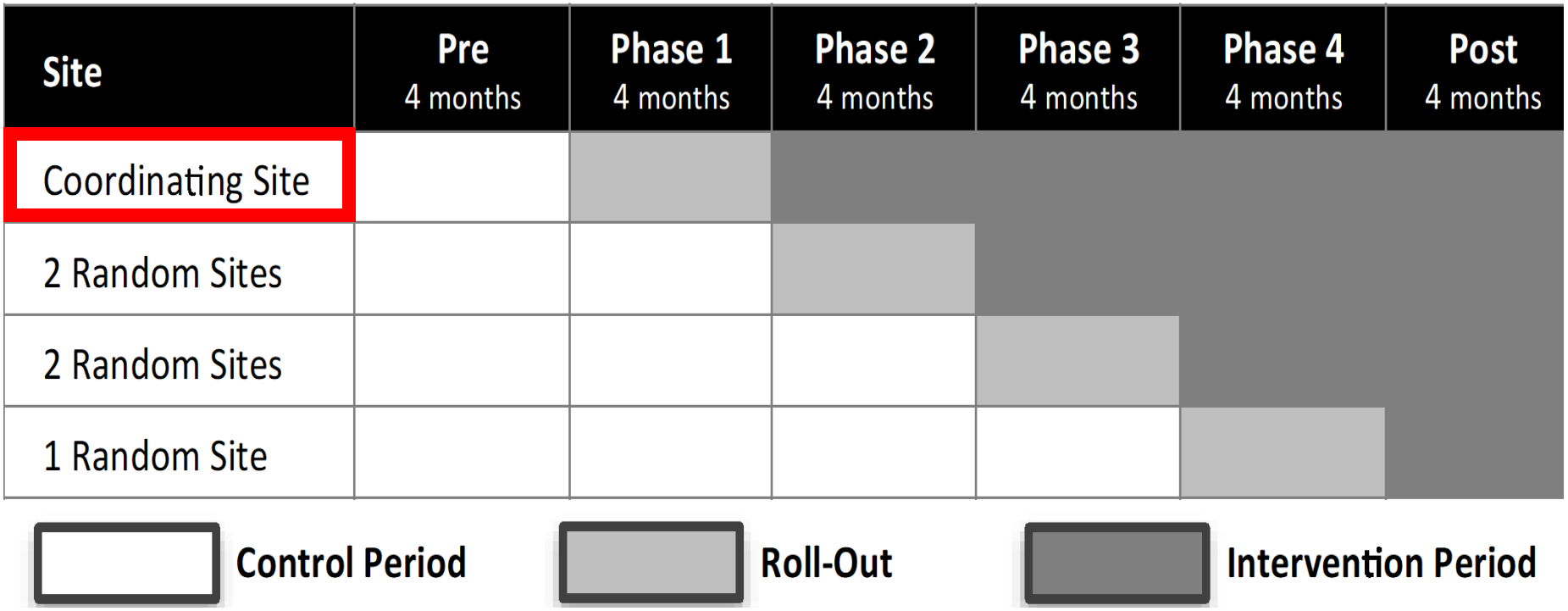


Study Designs for DECIDE-LVAD Trial

- 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 . . .

DECIDE-LVAD Trial

Figure 5. Stepped wedge randomization scheme.



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

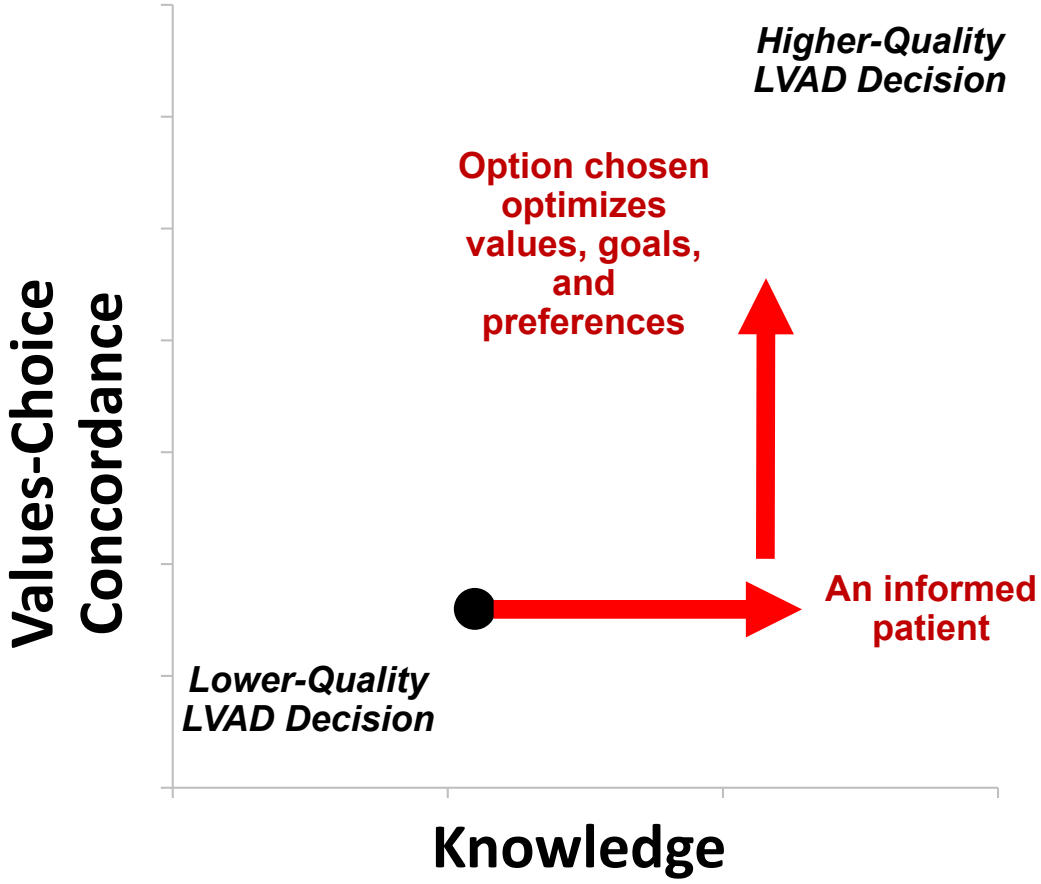
- Pre-implementation:
  - Planning, identifying key people

- 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”

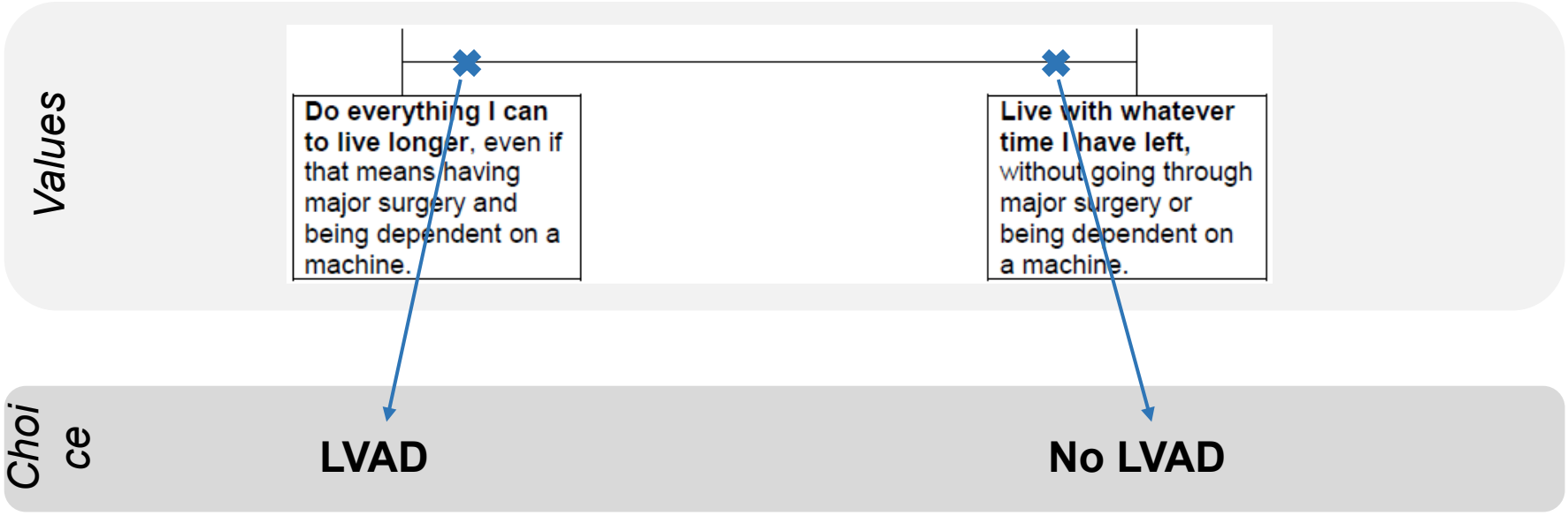
- Post-implementation
  - Ongoing site support
  - Follow-up visit

Primary Outcome: DECISION QUALITY

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

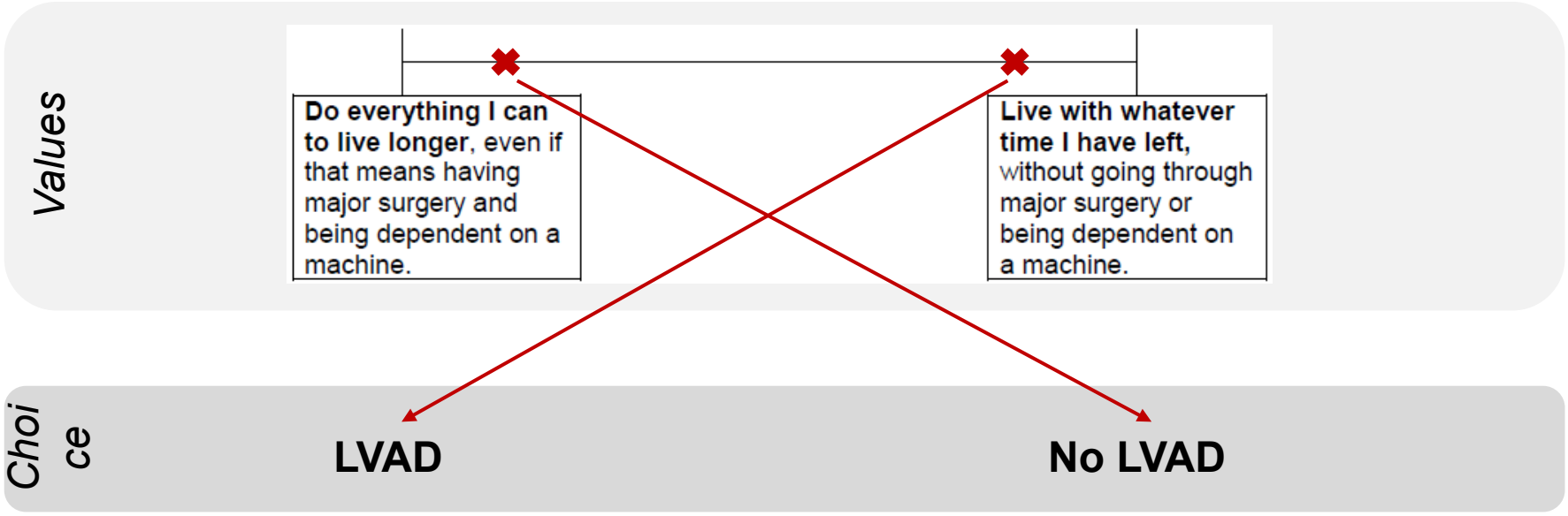


Values-Choice Concordance



Concordant

Values-Choice Concordance



Discordant

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%)

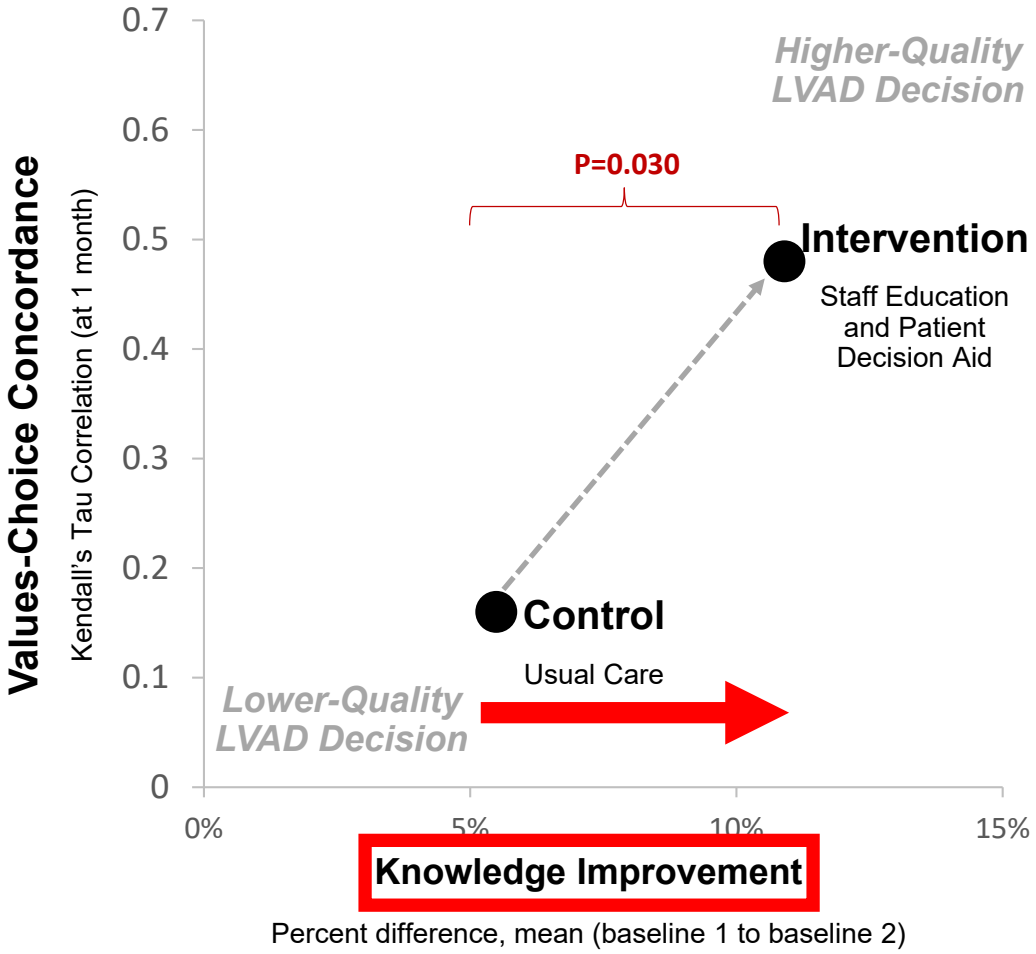
	Control (n=135)	Intervention (n=113)
Age, mean years (SD)	63.5 (9.7)	63.2 (10.2)
Male	82.2%	86.7%
White, non-Hispanic	79.1%	82.7%
Some college or more	56.4%	69.2%
On Disability	27.6%	32.0%
Married	72.5%	65.4%
Diagnosed < 2 years	11.9%	12.4%
Enrolled in ICU	21.5%	26.5%
INTERMACS 4-7 *(p<0.01)*	**18.3%**	**44.6%**

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)

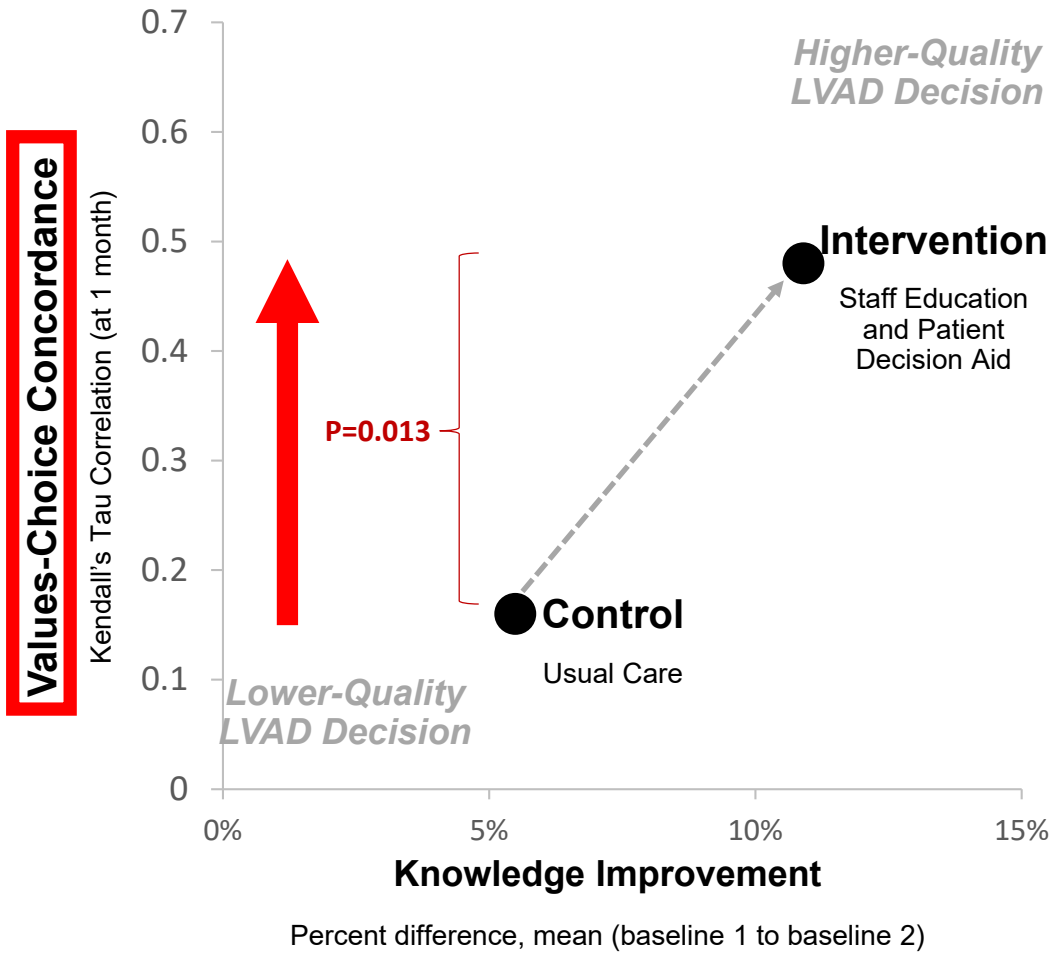
Knowledge

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

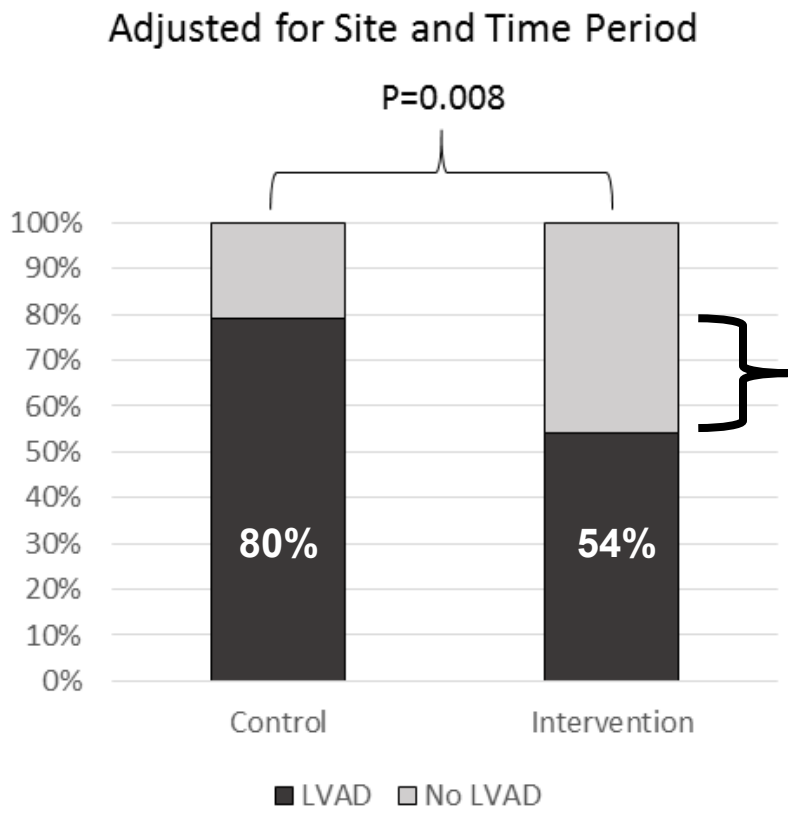


Values-Choice Concordance

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

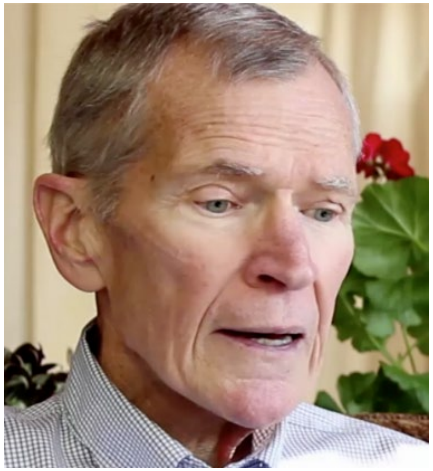


Secondary Outcomes: 6-month implant



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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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

	Time			
1	**2**	**3**	**4**	**5**
O	**X**	**X**	**X**	**X**
O	**O**	**X**	**X**	**X**
O	**O**	**O**	**X**	**X**
O	**O**	**O**	**O**	**X**

- 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

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:

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

Hussey & Hughes, *Contemp Clin Trials* 2007

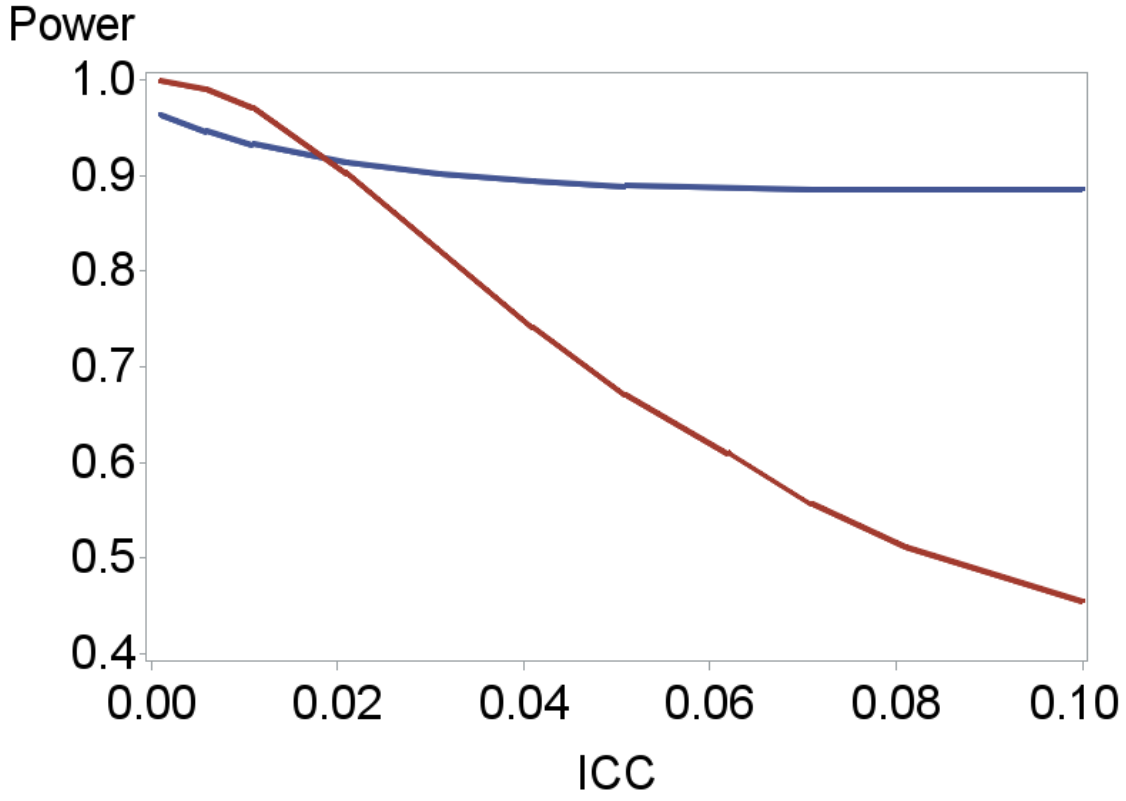
θ	treatment effect
β_j	time effects (constant across cluster)
$\alpha_i \sim N(0,\tau^2)$	between cluster variation
$e_{ijk} \sim N(0,\sigma^2)$	within cluster variation

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

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

Power – SW vs CRT

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



stepped wedge

cluster randomized

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

	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%
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

		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

Analysis Models

- GLMM
  - Unit of obs = Individual
  - Distributions – Normal, Binomial, Poisson, Cox
  - Hussey and Hughes
  - $f(Yijk) = \mu + \alpha_i + \beta_j + X_{ij}\theta + \varepsilon_{ijk}$
  - 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
  - deHoop (2015) BMC Med Res Method
  - 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?

Checklist: Feasibility of SW Design (2)

- ❑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: σ^2 (easy to know) ,τ^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)

	Time						
#	1	2	3	4	5	6	7
1	O	X	X	X	X	X	X
1	O	O	X	X	X	X	X
1	O	O	O	X	X	X	X
1	O	O	O	O	X	X	X
1	O	O	O	O	O	X	X
1	O	O	O	O	O	O	X

	Time			
#	1	2	3	4
2	O	X	X	X
2	O	O	X	X
2	O	O	O	X

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

	Time				
#	1	2	3	4	5
3	O	X	X	X	X
1	O	O	X	X	X
1	O	O	O	X	X
3	O	O	O	O	X

	Time				
#	1	2	3	4	5
2	O	X	X	X	X
2	O	O	X	X	X
2	O	O	O	X	X
2	O	O	O	O	X

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

	Time			
#	1	2	3	4
1	O	X	X	X
1	O	O	X	X
1	O	O	O	X

	Time				
#	1	2	3	4	5
1	O		X	X	X
1	O	O		X	X
1	O	O	O		X

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

	Time			
#	1	2	3	4
1	X	X	X	X
1	X	X	X	X
1	O	X	X	X
1	O	O	X	X
1	O	O	O	X
1	O	O	O	O
1	O	O	O	O

SW Power: Incomplete Designs

	Time			
#	1	2	3	4
1	O	X	X	X
1	O	O	X	X
1	O	O	O	X

	Time				
#	1	2	3	4	5
1	O	WR	X	X	X
1	O	O	WR	X	X
1	O	O	O	WR	X

Scenario	Total N	O or X N/cell	WR N/cell	*Power
Complete	840	20	NA	0.80
Incomplete	840	20	0	0.66
Partial	840	18	14	0.77
Incomplete	1176	28	0	0.79

*6 sites, 6 steps, alpha=0.05, ICC=0.1

SW Power/Sample Size Tools

Application	Notes
R: `swCRTdesign`	*Hughes J* 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
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