A pragmatic multi-center cluster randomized Study: Issues

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Design of a pragmatic multi-center cluster randomized study

- Focus: SPIRIT Trial, 2017-2022 (NIH R01 NR 017018)

PI: Mi-Kyung Song, PhD, RN, School of Nursing, Emory University

Design and Implementation Issues

Randomization and Sample size calculations

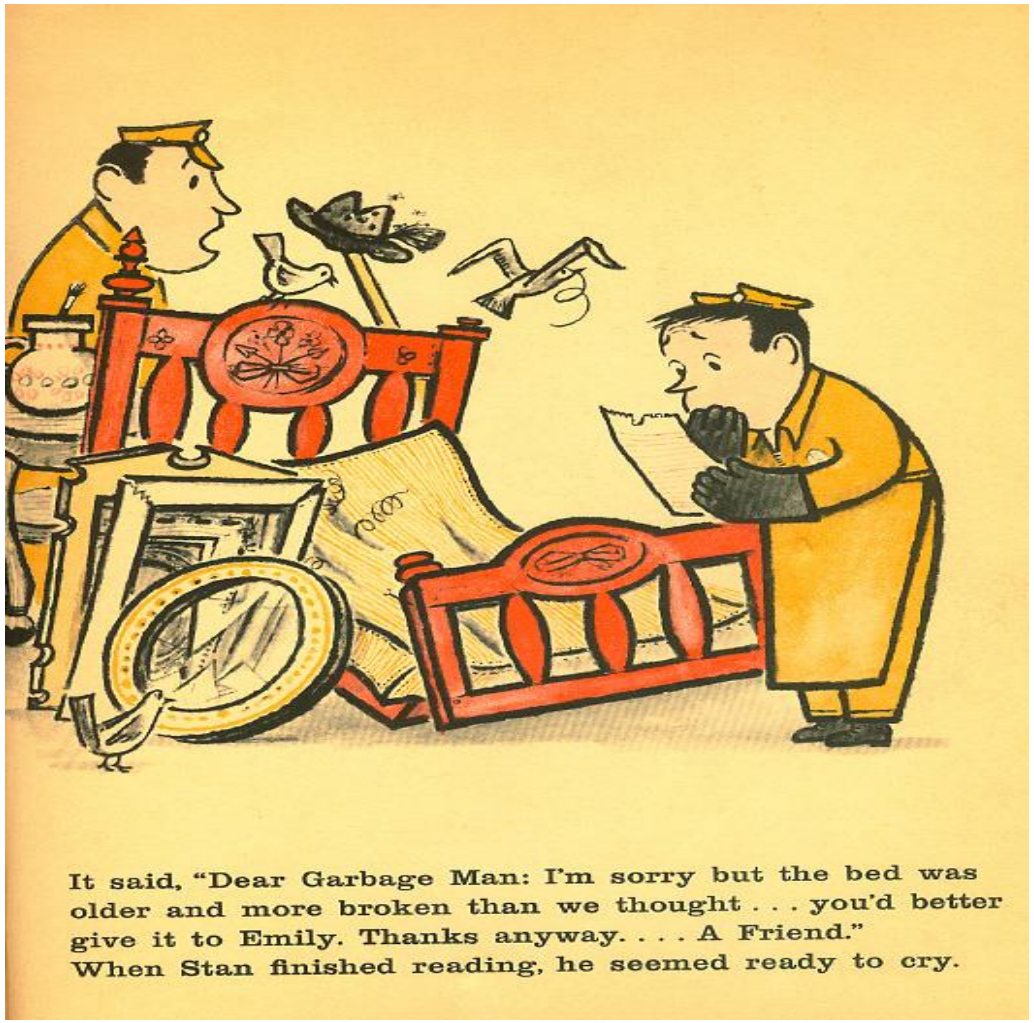
Pragmatic Clinical Trials: Testing treatments in the real world

Google Search resulted…….

“Pragmatic trials may test the same intervention as an explanatory trial, but they are conducted in real-world clinical practice settings, with typical patients and by qualified clinicians, who may not, however, have a research background”.

National Institute on Aging (https://www.nia.nih.gov/)

Garbage in and garbage out…..



Dear Garbage Man, 1957 [Painting]. (2008). In E. Avery (Author). Retrieved September 25, 2018

An Effectiveness-Implementation Trial of SPIRIT in End Stage Renal Diseases (ESRD)

- To examine the effectiveness of SPIRIT implemented as routine dialysis care

- To collect implementation data (e.g., care provider/staff acceptability, intervention fidelity, sustainability)

SPIRIT: An intervention for advanced care planning

Intervention: SPIRIT (Sharing Patient's Illness Representations to Increase Trust)?

- An advance care planning intervention designed and tested with the dialysis population (and other patient populations)

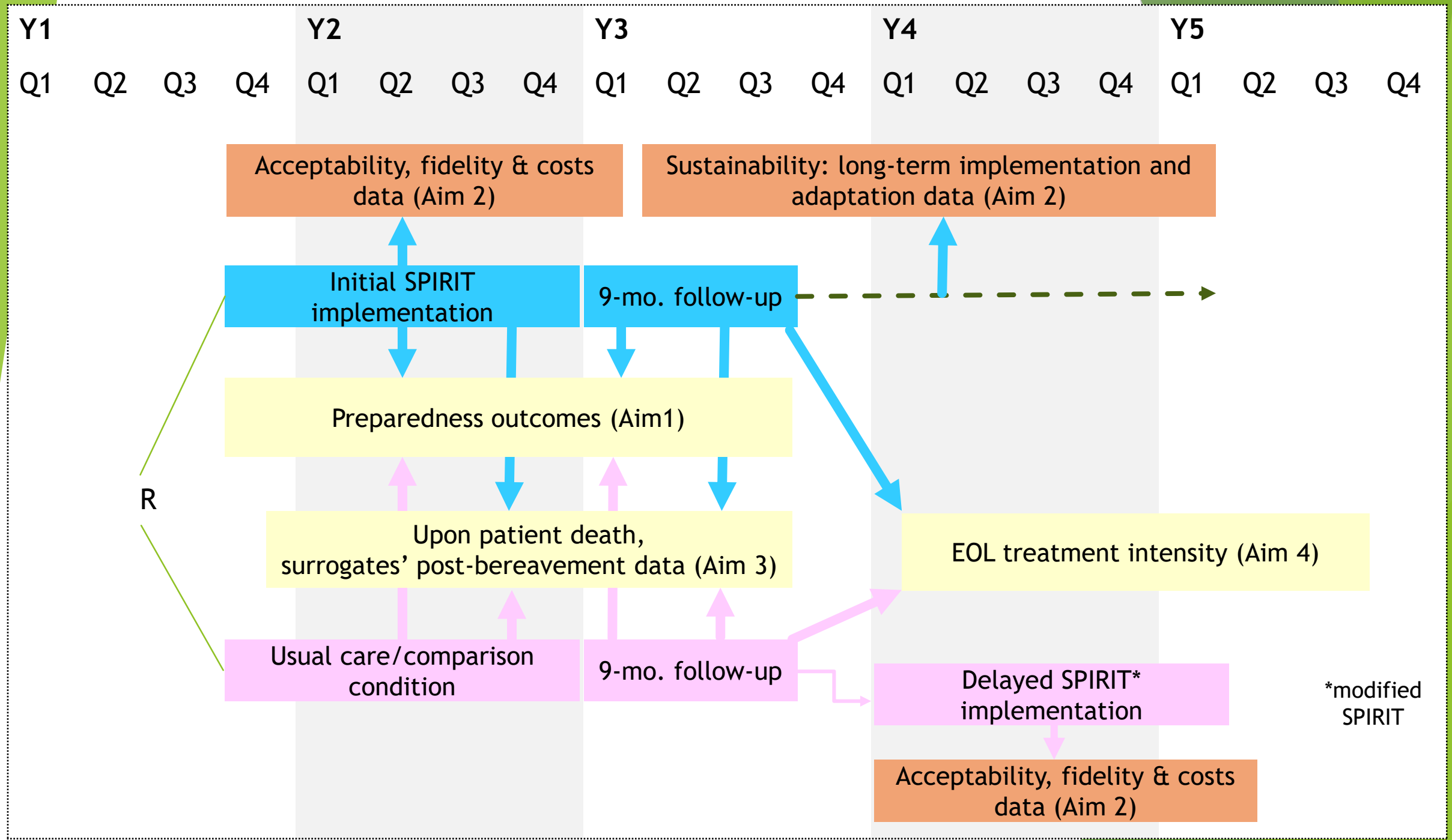
- The goal is to promote cognitive and emotional preparation for end-of-life decision making for patients on dialysis and their surrogates/family members
  - providing patients and families an opportunity to think about EOL care and promote authentic dialogues between the patient and the chosen surrogate
  - A preliminary study provided supporting evidence of SPIRIT for its effectiveness (Song el al. 2013)
- Structured interview format (using the SPIRIT Intervention Guide)

What is expected from Spirit?

- Improved preparedness for end-of-life decision making in patients and their surrogates
  - Patients clarify their EOL wishes with less difficulty
  - Surrogates understand those wishes and their role and responsibilities as a surrogate
- Improved bereavement outcomes for surrogates

Measureable Outcomes

- Patient-surrogate dyads' preparedness(Dyad congruence, decisional conflict, surrogate making confidence at 2 weeks post intervention)
- Surrogate post-bereavement outcomes (anxiety, depression, distress symptoms)
- End-of-life treatment intensity and consistency with wishes (health care utilization, hospitalization, length of hospital stay)


Y1
Y2
Y3
Y4
Y5
Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4
Acceptability, fidelity & costs data (Aim 2)
Sustainability: long-term implementation and adaptation data (Aim 2)
Initial SPIRIT implementation
9-mo. follow-up
Preparedness outcomes (Aim1)
R
Upon patient death, surrogates' post-bereavement data (Aim 3)
EOL treatment intensity (Aim 4)
Usual care/comparison condition
9-mo. follow-up
Delayed SPIRIT* implementation
Acceptability, fidelity & costs data (Aim 2)
*modified SPIRIT

Study coordination

Site coordinator training
Randomization
SPIRIT training
Site orientation
Recruitment monitoring
Fidelity monitoring
Effectiveness data collection
Medicare claims data acquisition

Emory University School of Nursing

Independent DSMB

Data and safety monitoring
Data management
Data cleaning
Data analysis

REDCap Research Electronic Data Capture

Local research teams

Site orientation, recruitment, EHR abstraction, fidelity monitoring, implementation data collection, contextual data collection

Emory

UNM

Pitt

UNC

Study clinics

Clinic #1	Clinic #4	Clinic #7	Clinic #10	Clinic #13	Clinic #16	Clinic #18	Clinic #20	Clinic #22	Clinic #24	Clinic #26	Clinic #28
Clinic #2	Clinic #5	Clinic #8	Clinic #11	Clinic #14	Clinic #17	Clinic #19	Clinic #21	Clinic #23	Clinic #25	Clinic #27	Clinic #29
Clinic #3	Clinic #6	Clinic #9	Clinic #12	Clinic #15							Clinic #30

Patient screening, SPIRIT implementation

Eligibility for the study

- All modalities (HD, nocturnal HD; PD, home HD)
- Exclusion criteria
  - Cognitive impairment (based on clinician's judgment)
  - Currently enrolled in hospice

- Inclusion:
  - Must have an available surrogate decision maker
  - Meeting the Surprise Question, well-validated for ESRD

Eligibility - “Pragmatic”

- Meeting the Surprise Question (well-validated for ESRD)

- A clinician asks herself,

“Would I be surprised if this patient dies in the next year?”

If the answer is “no”, the patient is meeting this criterion

Charlson Comorbidity Index is recommended but….

Time consuming

Not practical in real world

Flexibility in delivering intervention -”pragmatic”

- Surrogate wishes to participate in the study but the SPRIT intervention cannot be applied in a face-to-face meeting

- Alternative: Video conferencing (not yet validated)

Is the video conferencing as effective as the face-to-face session?

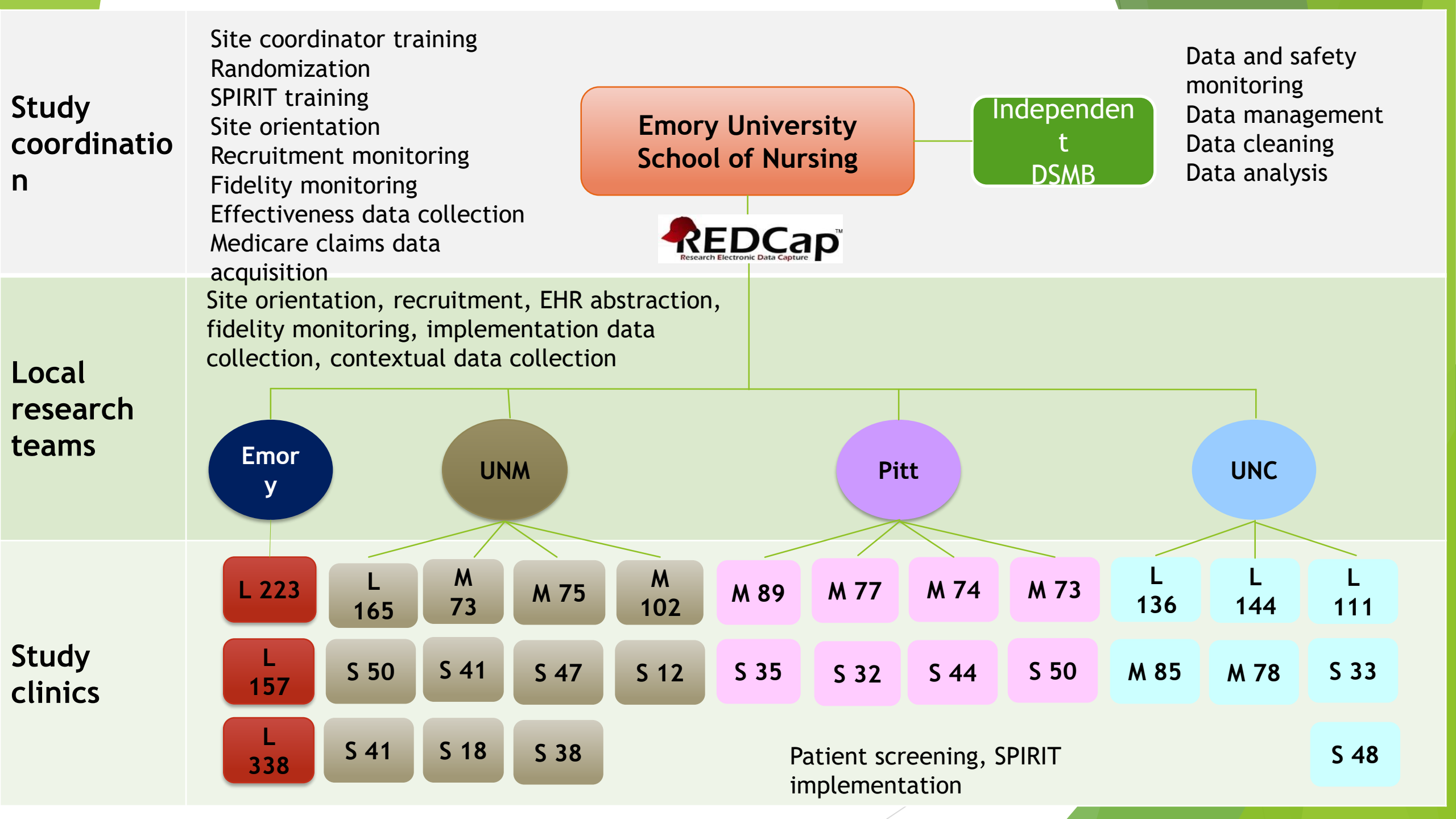
Difficult Decisions with pragmatism

- Deviations from the protocol (e.g. subjects are not available for measurements etc.)
- Compromising internal validity
- Threats to Internal Validity: Confounding, Measurement Error, Consistency in the application of intervention/instrument change, Selection of subjects etc.
- Key: To balance the act between internal validity vs flexibility of the trail being close to a real world.

Randomization

- Dialysis units are randomized within each State because
  - The intervention is naturally applied at the dialysis unit level
  - To avoid intervention (SPIRIT) contamination to the placebo (usual care) group
- Factors in Consideration : State, Race, Size

  Complication: Champion applies the intervention but in some cases, the same champion may attend two units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Study clinics
L 223
L 165
M 73
M 75
M 102
M 89
M 77
M 74
M 73
L 136
L 144
L 111
L 157
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M 78
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Patient screening, SPIRIT implementation
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Common champion for 2 clinics

Common champion for 3 clinics

Emory | UNM | Pitt | UNC

Study clinics

Emory	UNM				Pitt				UNC		
L 223	L 165	S 47	S 12	M 102	M 89	M 77	M 74	M 73	L 136	L 144	L 111
L 157	S 50	S 41	M 75	M 73	S 35	S 32	S 44	S 50	S 33	S 48	M 85
L 338	S 41	S 18	S 38								M 78

Patient screening, SPIRIT implementation

Balance with the randomization

Randomize the clinics within State while assigning the same condition for units that share champions and keeping the balance of the size of clinic (L, M, S) and intervention (Spirit vs usual care)

	T	C	Total
L	4	3	7
M	5	4	9
S	6	7	13
Total	15	14	29

By Size

	T	C	Total
GA	2	1	3
UNM	5	6	11
PITT	4	4	8
NC	4	3	7
Total	15	14	29

By State

Sample Size Calculation (Power?)

- If each cluster(cinic) of which contains same number of individuals, i.e., $n_{ik} = n$, the total number of cluster per arm for comparing two group means ($H_0: \mu_1 = \mu_2$ vs. $H_0: \mu_1 \neq \mu_2$) has the form:

$$m = \frac{2(z_{1-\alpha/2} + z_{1-\beta})^2 \sigma^2 \{1 + (n-1)\rho\}}{(\mu_1 - \mu_2)^2 n}$$

- If each cluster has different size, n_{ik} that is i.i.d with $E(n_{ik}) = \theta$, $Var(n_{ik}) = \tau^2$, the total number of cluster per arm by accounting for variability due to cluster size has the form:

$$\mathrm{m} = \frac{2(z_{1-\alpha/2}+z_{1-\beta})^2 \sigma^2}{(\mu_1-\mu_2)^2} \left\{ (1-\rho)\frac{1}{\theta} + \rho + \rho\gamma^2 \right\},$$

where $\gamma = \tau/\theta$ denotes the coefficient of variation of cluster size

(Manatunga et al. 2001).

Model (Power based on Simulations)

$$Y_{ijk} = \mu + \alpha_i + \beta_{j(i)} + \gamma z_{j(i)} + \epsilon_{ijk}$$

- μ: Grand mean
- α_i: Effect of ith state
- $\beta_{j(i)}$: Random effect of jth clinic in ith state distributed as N(0, σ_β^2)
- γ: Intervention (treatment) effect
- $z_{j(i)}$: Indicator of intervention or control status for jth clinic in ith state
- ϵ_{ijk}: Random error term distributed as N(0, σ_ϵ^2)

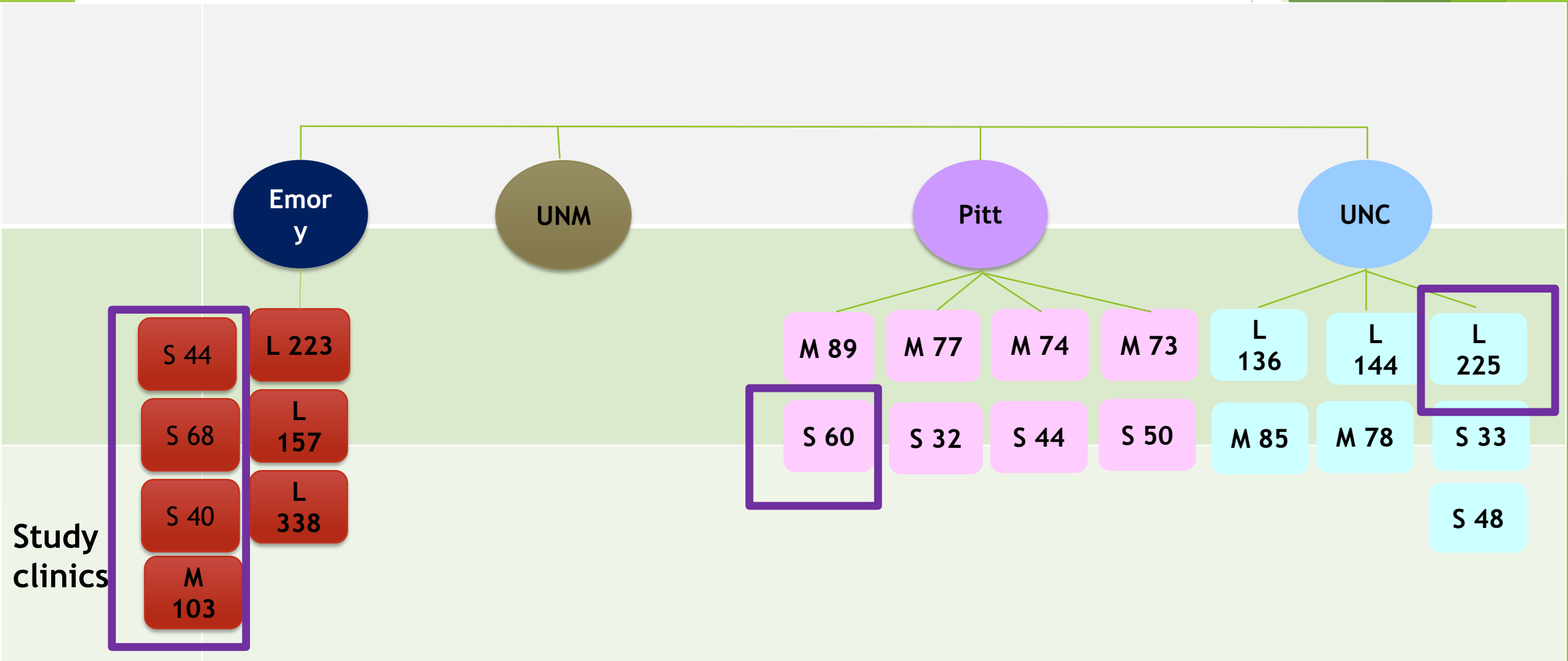
Power calculations

- Participation rate on average 20%
- The response rate (Dyad Congruence) for the control group 48% (Song et al 2013)
- With 29 dialysis units
- Interclass correlation 0.04-0.02

- To detect an odds ratio of 2.0, the study will have 84%- 92%

- For the post-bereavement outcome (continuous) variables, HADS-anxiety, HADS-depression, and PTSS-10 , we have adequate power (80-85%) for meaningful differences (we anticipate 40% patient's death and hence estimated power is based on an anticipated sample size 160.

The real-life trial



Power calculations

- The response rate (Dyad Congruence) for the control group 48% (Song et al 2013)
- With 22 dialysis units
- Interclass correlation 0.04-0.02
- To detect an odds ratio of 2.0, the study will have 84%- 92% (approx. 79%-87%)
- For the post-bereavement outcome (continuous) variables, HADS-anxiety, HADS-depression, and PTSS-10 , we have adequate power (80-85%) (77%-83%) for meaningful differences.

Methodological Issues

- Is there a better method for randomizing while balancing the size of the clinic?
- Staggered entry of States to the trial and number of clinics change etc.. Is there a better way of randomizing?
- How to accommodate different champion effects in the same clinic?
- Given that intervention is delivered in “face-to-face” vs video. A small validation study might help in estimating true effects and increasing power.
- How much variability in the “surprising question” (exclusion criteria). What does this mean? What is the inferential population?

Design Issues

- Dropping out clusters in cluster randomized studies lead to serious consequences (under power, lack of resources to recruit additional clusters, time spent etc.)
- Experiences with research studies help and commitments should be clear and explicit
- “real world” aspects bring more complications to study designs (e.g. champions are employed by the dialysis clinics, changing staff etc.)
- “real world” aspects bring more complications to analyses and interpretations (missing data, measurement error in outcomes (Medicare claim data)etc.)

Goal: To addresses the objective of the trial including its ability to inform clinical practice

It is a balancing act!! (flexibility vs integrity of the trial)

(Plus Images · Pixabay · Download Free Pictures

- Important: Documentations with justifications are needed throughout the trial to maintain high quality.

Acknowledgement

- Many thanks to Dr. Song and her study data coordinator, Mary Laszlo

- Several Slides regarding the study design are borrowed from Dr. Song.

References

- Mi-Kyung Song, Mark L Unruh, Amita Manatunga, Laura C. Plantinga, Janice Lea, Manisha Jhamb, Abhijit V. Kshirsagar, Sandra E. Ward. SPIRIT Trial: A Phase III Pragmatic Trial of an Advance Care Planning Intervention in ESRD. Contemp Clin Trials. 2018 Jan; 64: 188–194.

- Process and impact of an advance care planning intervention evaluated by bereaved surrogate decision-makers of dialysis patients. Palliative Medicine, 2013,31(3), 267-274

- Manatunga, A.K., Hudgens, M., Chen, S. Sample Size Estimation in Cluster Randomized Studies With Varying Cluster Size. *Biometrical Journal* (2001), 43(1): 75-86.

NEW

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