

# From Prescriptive to Pragmatic: Clinical Trial Designs in Palliative Care

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**THE NYU RORY MEYERS COLLEGE OF NURSING**





## On the Docket

- How prescribed are you going to be? (Prescriptive → Pragmatic)
- Recruitment and Retention
- Ethical Issues
- Emerging Designs





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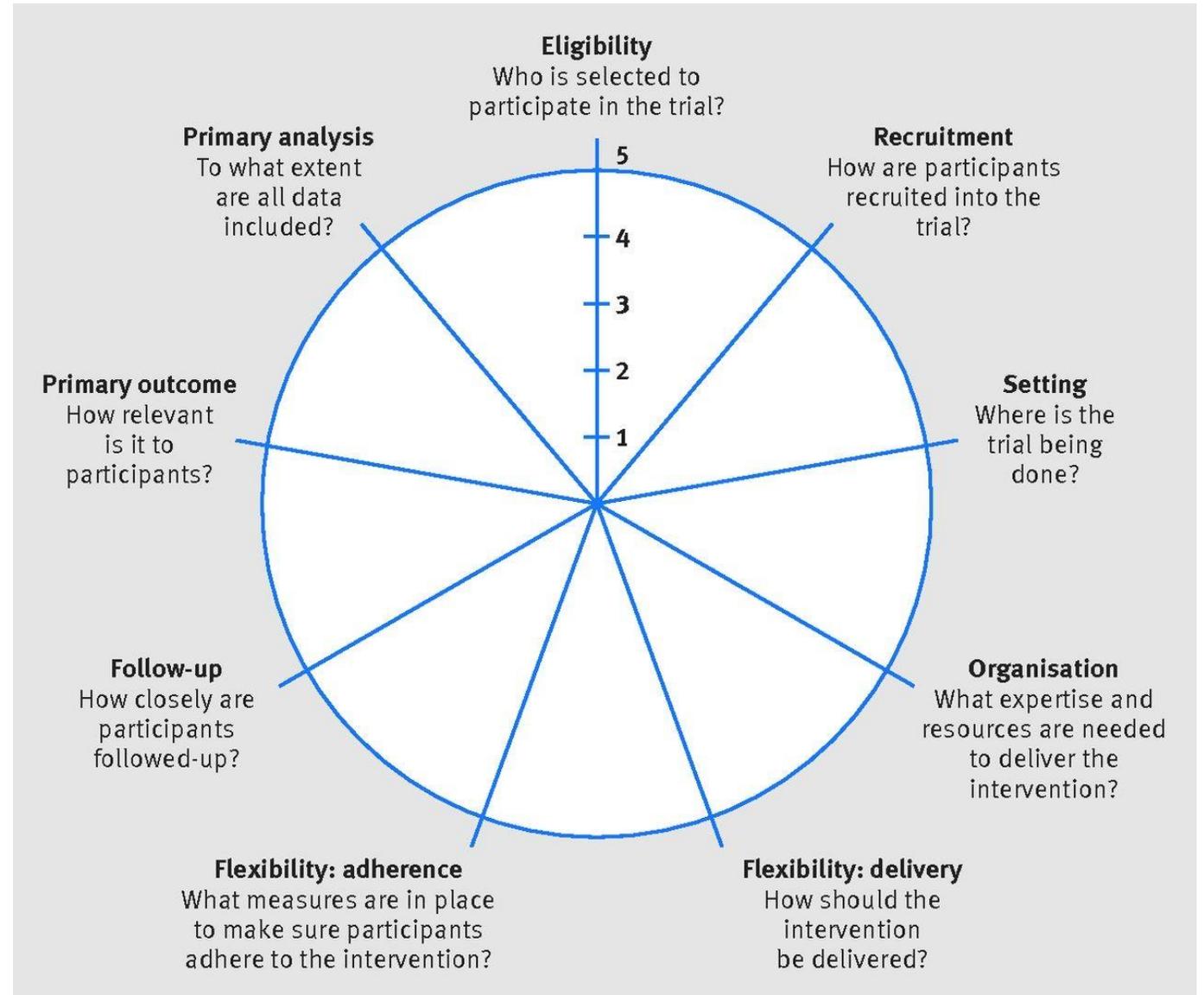
**Table 1 | Key differences between trials with explanatory and pragmatic attitudes, adapted from a table presented at the 2008 Society for Clinical Trials meeting by Marion Campbell, University of Aberdeen**

Question	Efficacy—can the intervention work?	Effectiveness—does the intervention work when used in normal practice?
Setting	Well resourced, “ideal” setting	Normal practice
Participants	Highly selected. Poorly adherent participants and those with conditions which might dilute the effect are often excluded	Little or no selection beyond the clinical indication of interest
Intervention	Strictly enforced and adherence is monitored closely	Applied flexibly as it would be in normal practice
Outcomes	Often short term surrogates or process measures	Directly relevant to participants, funders, communities, and healthcare practitioners
Relevance to practice	Indirect—little effort made to match design of trial to decision making needs of those in usual setting in which intervention will be implemented	Direct—trial is designed to meet needs of those making decisions about treatment options in setting in which intervention will be implemented



# Pragmatism PRECIS-2

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*The* NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

## Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A.,  
Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H.,  
Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N.,  
Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H.,  
J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

More  
Prescriptive



## More Prescriptive (but still kind of pragmatic)

- Eligibility-Metastatic NSLC
- Recruitment-Through oncologist referral, traditional RCT 1:1
- Setting-Single academic medical center
- Organization-Single Palliative Care Team
- Flexible Delivery- semi-flexible protocol with domains to address
- Flexible Adherence-Scheduling at same time of onc visit
- Follow-up-All data must be collected in a +/- 3wk window
- Primary Outcome Relevance to Pt-FACT-L (QOL)
- Primary Analysis-All participant data included, imputed for missing patients



# More Prescriptive

## 5.2.2. Inclusion Criteria

1. histologically or cytologically confirmed incurable NSCLC, stage IIIB with a pleural or pericardial effusion or stage IV,
2. performance status 0-2,
3. diagnosis of advanced NSCLC within the previous eight weeks,
4. ability to read and respond to questions in English, and
5. permission of attending physician.

## 5.2.3. Exclusion criteria

1. prior chemotherapy for metastatic disease, or
2. the existence of other co-morbid disease, which in the opinion of the investigator prohibits participation in the protocol.





# More Prescriptive

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# More Pragmatic

## BMJ Open Primary Palliative Care for Emergency Medicine (PRIM-ER): Protocol for a Pragmatic, Cluster-Randomised, Stepped Wedge Design to Test the Effectiveness of Primary Palliative Care Education, Training and Technical Support for Emergency Medicine

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Corita R Grudzen,<sup>1,2</sup> Abraham A Brody,<sup>3</sup> Frank R Chung,<sup>1</sup> Allison M Cuthel,<sup>1,2</sup>  
Devin Mann,<sup>2,4</sup> Jordan A McQuilkin,<sup>1</sup> Ada L Rubin,<sup>1</sup> Jordan Swartz,<sup>1</sup> Audrey Tan,<sup>1</sup>  
Keith S Goldfeld,<sup>2</sup> The PRIM-ER Investigators

# More Pragmatic

- Eligibility-30% mortality risk on claims, community dwelling
- Recruitment-No recruitment, uses secondary data, stepped wedge trial → unit of analysis is the ED
- Setting-35 Academic Emergency Rooms
- Organization-All except 1 have EPIC, All are academic medical centers with strong ER leaders
- Flexible Delivery- flexible in how training is done for nurses and physicians, flexible in how CDS is implemented
- Flexible Adherence-Measure of completion of intervention, use of CDS
- Follow-up-None, use of secondary data for outcomes from Medicare
- Primary Outcome Relevance to Pt-Acute Care Admission
- Primary Analysis-All participant with complete Medicare files (No Medicare Advantage)





# Recruitment

- What is the milieu you are recruiting from?
  - Academic vs non-academic, resources available
  - Community vs Acute
  - What referral processes might work?
- Level of illness of the potential subject
- Cognition
- Diversity of Populations
- Rapidly update your recruitment plan if it's not working, don't wait
- Language Matters



# Retention

- Reminders
- Incentives
- Magnets or other physical reminders
- Send birthday/holiday cards from the stu
- Time period measurement flexibility
- Nights and Weekends



Research  
Coordinator: \_\_\_\_\_

Telephone: \_\_\_\_\_

Visit 1: \_\_\_\_\_

Visit 2: \_\_\_\_\_

Visit 3: \_\_\_\_\_

Visit 4: \_\_\_\_\_



## Ethical Issues

### **Feeling guilty about randomizing to a control arm? DON'T**

- WHY do the trial if there's evidence that something is superior?
- We only do trials because there ISN'T good evidence of something!
- Patient's can always decline to participate (becomes retention issue after randomization)
- In certain studies, particularly individually randomized in upstream PC, can waitlist control (can enhance retention)





## Emerging Designs

- Cluster Randomization
- Stepped Wedge Design
- Adaptive, SMART and MOST Designs
- N of 1 Trials





# Cluster Randomization

- Used when wishing to perform an RCT in a setting where you can't randomize the patient
  - To avoid contamination → CAREFUL what your cluster is (unit vs site)
  - Because the intervention has to be carried out in a set area
- Requires calculation of ICC
- Challenges
  - Usually requires at least 16 clusters if not more
  - Matching or stratification of clusters





# Cluster Randomization-PROVEN

## **Pragmatic Trial of Video Education in Nursing Homes (Mor, Mitchell, Volandes)**

- Conducted in 360 nursing homes (N=119 intervention/N=241 control) owned by two healthcare systems. Randomized at the Facility Level 1:2
- Intervention facilities instructed to offer the Advance Care Planning Video Program to all patients.
- Patient characteristics and outcomes were ascertained from Medicare Claims, Minimum Data Set assessments, and facility electronic medical record data.
- Intervention adherence was measured using a Video Status Report embedded into electronic medical record systems.
- The primary outcome was the number of hospitalizations/person-day alive among long-stay patients with advanced dementia or cardiopulmonary disease.





# Stepped Wedge Trial

- A cluster type trial used when you can't do straight cluster randomization

## PROs:

- Easier to recruit sites because all sites serve as intervention
- Greater power than traditional Cluster RCT

## CONs:

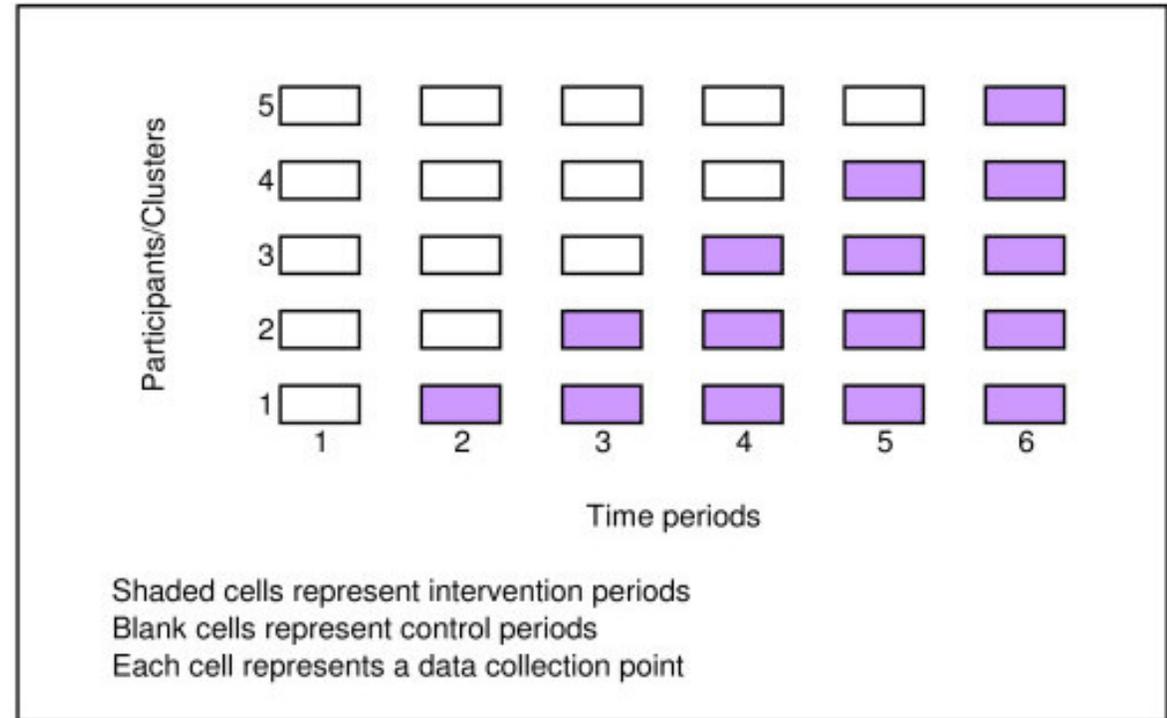
- No true current control group; each site acts as its own pre-post control
- Statistics are more complex
- Harder to interpret

NOTE: Needing to space out implementing an intervention is not a reason to do stepped wedge, this can be done in a traditional cluster RCT where you slowly implement over time.



# Stepped Wedge Trial

- X# of clusters receives the intervention in each time period
- Order is through randomization
- Everyone gets intervention by end of study



# Stepped Wedge Trial



## PCRC Investigator Development Center Webinar Series

### **“Stepped Wedge Trial Design”**

**Host:** Diane Fairclough, DrPH, MSPH, MS will be leading the September webinar, titled: **"Stepped Wedge Trial Design."** Dr. Fairclough is a professor in the Department of Biostatistics and Informatics in the Colorado School of Public Health and director of the Biostatistics Core of the Colorado Health Outcomes Program at the University of Colorado in Denver.

**When:** Monday, September 23<sup>rd</sup>, 2019 at 1pm Eastern Time

**Registration Required:** Click the blue button to register for the webinar



## Adaptive and SMART Designs

- Adaptive Interventions are individually tailored sequences of interventions, with treatment type and dosage changing according to patient outcomes.
- Operationalize clinical practice.





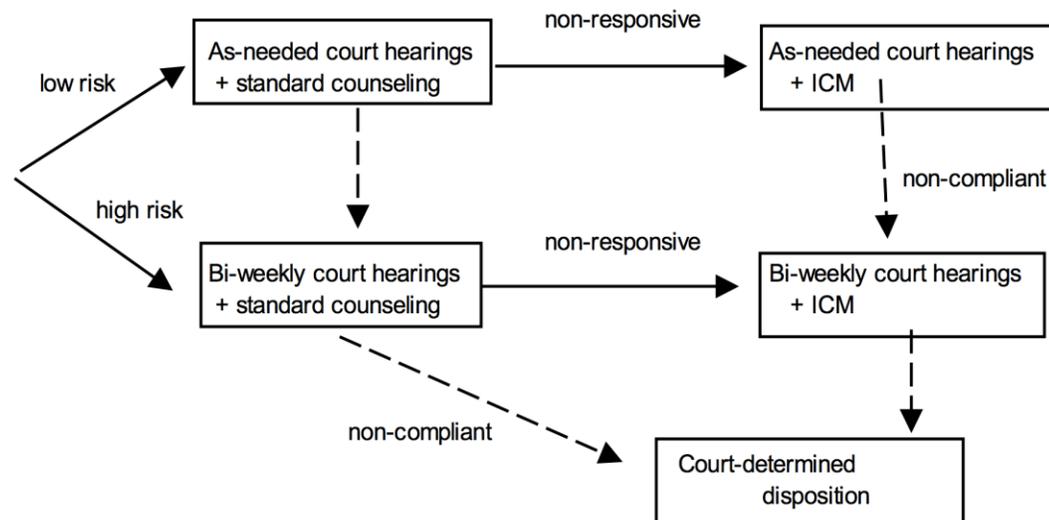
## Why Adaptive Interventions?

- High heterogeneity in response to any one treatment
- What works for one person may not work for another
- What works now for a person may not work later (and relapse is common)
- Lack of adherence or excessive burden is common
- Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient



# Adaptive Trial (not in palliative care) as illustration

- Adaptive Drug Court Program for drug abusing offenders.
- Goal is to minimize recidivism and drug use.
- Marlowe et al. (2008, 2009, 2012)



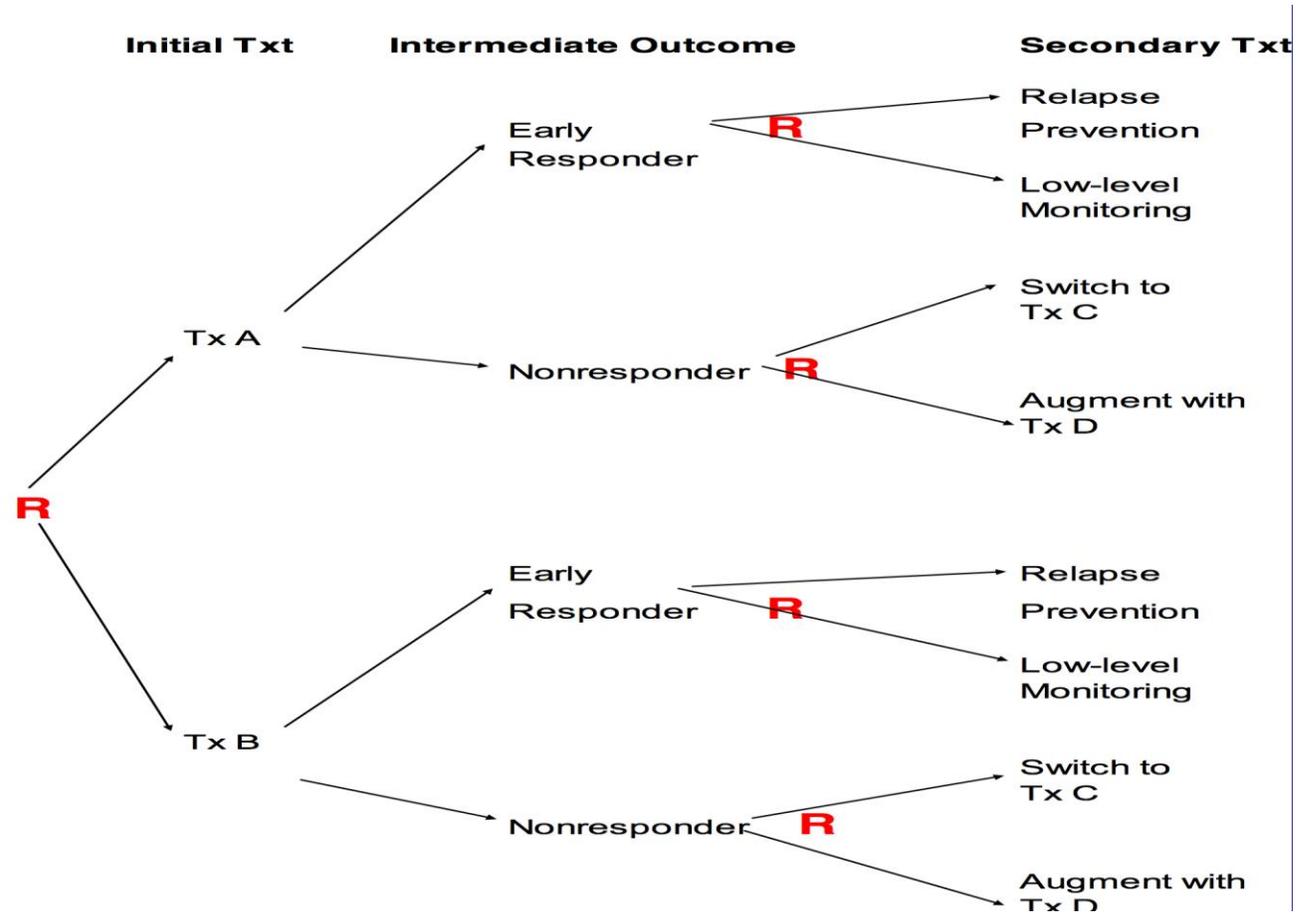


## Key Decisions in Adaptive Design

- What is the best sequencing of treatments?
- What is the best timings of alterations in treatments?
- What information do we use to make these decisions? (how do we individualize the sequence of treatments?)



# SMART Design



# SMART Design



## PCRC Investigator Development Center Webinar Series

### **“SMART Design to Answer Important Questions in Palliative Care”**

**Host:** Tamara Somers, PhD, Marie Davidian, PhD, and Eric Laber, PhD, will be co-leading the July webinar, titled: **“SMART Design to Answer Important Questions in Palliative Care”**. Dr. Somers is a clinical psychologist in the Department of Psychiatry and Behavioral Sciences at Duke University. Dr. Davidian is a professor, and Dr. Laber an associate professor, in the Department of Statistics at North Carolina State University.

**When:** Tuesday, July 9th, 2019 at 4pm Eastern Time

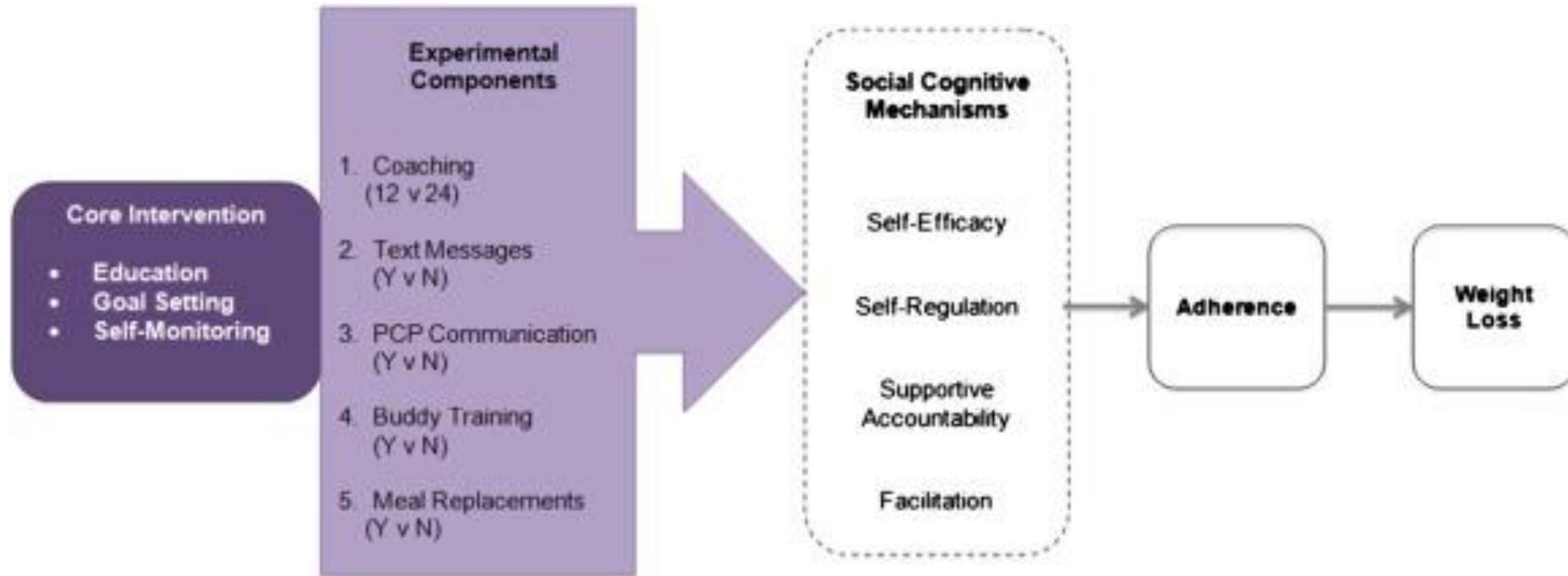


# MOST Design

- Multiphase Optimization Strategy (MOST)
- RCTs traditionally evaluate a whole intervention
- MOST evaluates the components that are most important/effective
- Performed before an effectiveness RCT
- Can be used to optimize an intervention and understand the key programmatic and delivery components.



# MOST Design



# MOST Design

## 2.3. Study design

A complete factorial experiment would have required implementation of 32 experimental conditions. To conserve resources, we selected a fractional factorial design that involves 16 experimental conditions (Table 2) [26].<sup>1</sup> It is important to note that although there are 16 experimental conditions, this experiment should not be considered a 16-arm RCT.

The purpose of this factorial experiment is to estimate the main effects of the five intervention components and interactions between the components, not to compare the 16 experimental conditions to each other. Each main effect and interaction estimate is based on all of the experimental conditions, and therefore on all of the participants. For example, the main effect of the number of coaching sessions will be estimated by comparing the mean of experimental conditions 1–8 in Table 2 vs. the mean of experimental conditions 9–16. For a more detailed explanation of how a factorial experiment maintains power for estimation of main effects and interactions, see [11].

Table 2.  
Experimental conditions.

Experimental condition	CORE	# Coaching sessions	Progress report to PCP	Text messages	Meal replacement recommendation	Buddy training
1	Yes	12	Yes	No	No	No
2	Yes	12	Yes	No	Yes	Yes
3	Yes	12	Yes	Yes	No	Yes
4	Yes	12	Yes	Yes	Yes	No
5	Yes	12	No	No	No	Yes
6	Yes	12	No	No	Yes	No
7	Yes	12	No	Yes	No	No
8	Yes	12	No	Yes	Yes	Yes
9	Yes	24	Yes	No	No	No
10	Yes	24	Yes	No	Yes	Yes
11	Yes	24	Yes	Yes	No	Yes
12	Yes	24	Yes	Yes	Yes	No
13	Yes	24	No	No	No	Yes
14	Yes	24	No	No	Yes	No
15	Yes	24	No	Yes	No	No
16	Yes	24	No	Yes	Yes	Yes

Table options ▼

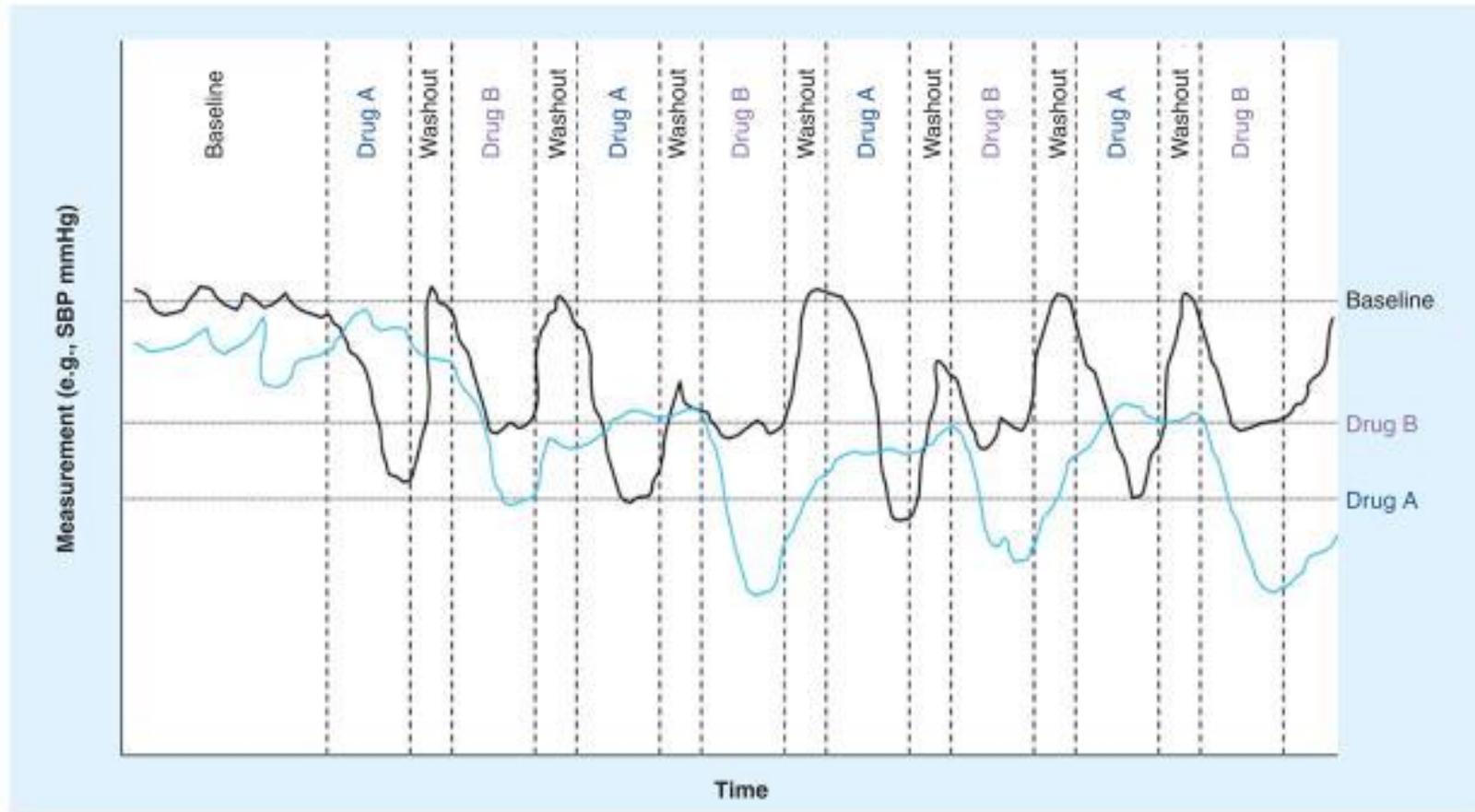


## N of 1 Trial

- Used in many early stage behavioral interventions
- In such trials, the patient undergoes pairs of treatment periods organized so that one period involves the use of experimental treatment and the other involves the use of an alternate or placebo therapy.
- The patient and clinician are blinded, if possible, and outcomes are monitored.
- Treatment periods are replicated until the clinician and patient are convinced that the treatments are definitely different or definitely not different.
- Good for Personalized Treatment



# N of 1 Trial



# N of 1 Trial Example

*J Pain Symptom Manage.* 2015 Sep;50(3):289-96. doi: 10.1016/j.jpainsymman.2015.03.009. Epub 2015 Apr 18.

## **The Effect of Methylphenidate on Fatigue in Advanced Cancer: An Aggregated N-of-1 Trial.**

Mitchell GK<sup>1</sup>, Hardy JR<sup>2</sup>, Nikles CJ<sup>3</sup>, Carmont SA<sup>3</sup>, Senior HE<sup>3</sup>, Schluter PJ<sup>4</sup>, Good P<sup>5</sup>, Currow DC<sup>6</sup>.

### **⊕ Author information**

#### **Abstract**

**CONTEXT:** Fatigue is common in life-limiting cancer. Methylphenidate (MPH), a psychostimulant, may be a useful therapy. Gathering evidence in patients with advanced cancer can be challenging.

**OBJECTIVES:** To determine if MPH improves cancer-related fatigue in people with advanced cancer.

**METHODS:** N-of-1 trials are multicycle, double-blind, randomized, controlled crossover trials using standardized measures of effect in individuals. They are normally used to assess treatment effects in individuals. Aggregated N-of-1 trials from participants with end-stage cancer suffering fatigue were used to assess the group effect of MPH, producing an estimate of equivalent power to a parallel-group randomized controlled trial (RCT) but requiring less than half of the sample size. Up to three cycles of MPH 5 mg twice daily (three days) vs. identical placebo (three days) capsules were offered to participants. Primary outcome was improvement in fatigue as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue Scale and the Wu Cancer Fatigue Scale. Analysis used Bayesian statistical methods using intention-to-treat principles.

**RESULTS:** Forty-three participants completed 84 cycles of MPH and placebo in random order, exceeding sample size estimates. Overall, MPH did not improve fatigue (mean difference 3.2; 95% credible interval -2.0, 9.0; posterior probability of favorable effect 0.890). Eight participants showed important improvement, and one participant showed important worsening of fatigue on MPH. There were no features that distinguished participants whose fatigue responded to MPH compared with those who did not.

**CONCLUSION:** MPH does not improve fatigue in the population of patients with end-stage cancer. Aggregated N-of-1 trial methodology is feasible and produces population-based sample estimates with less than half the sample size required for the equivalent parallel-group RCT. It also identified individuals who did and did not respond to MPH, which is a feature difficult to achieve in a standard RCT. The study was registered with the Australian Clinical Trials Registry (12609000794202).

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**KEYWORDS:** Methylphenidate; N-of-1 trial; advanced cancer; fatigue; palliative care



# Resources

- Palliative Care Research Cooperative-Webinars, Training Intensive, F2F Meeting
- State of the Science in Palliative Care at end of Annual Assembly (2020)
- NIH Healthcare Systems Collaboratory (and its living textbook)
- Clinicaltrials.gov and Protocol Papers → DIG INTO THE DETAILS
  - Look at successful and unsuccessful trials from recruitment standpoint especially
- CTSIs often have significant resources for training

