University of Pittsburgh

Design considerations for clinical trials of non-pharmacological interventions

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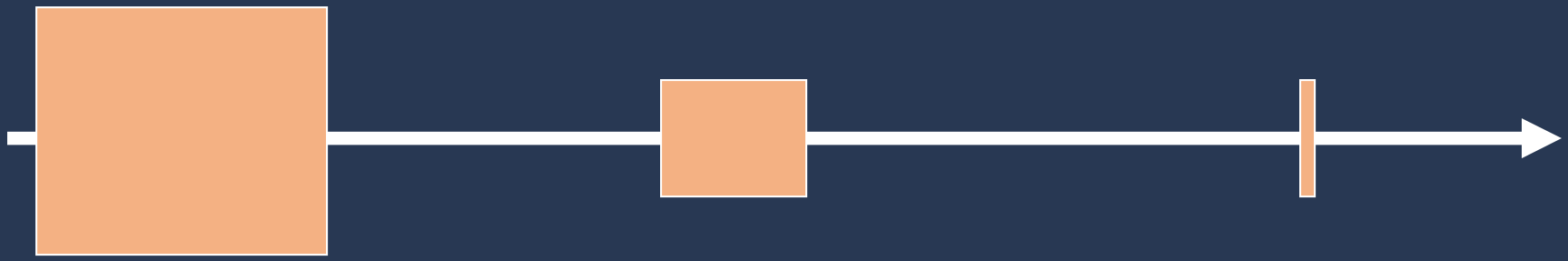
Outline

- My experience with NP trials
- Multi-modal interventions
- Usual care as a control
- CONSORT NP extension

Drug trials: Staging



Phase I:

dose & safety

outcome:
toxicity PK/PD

Phase II:
efficacy & safety

outcome:
short-term
surrogate
futility trials

Phase III:
efficacy/
effectiveness

outcome:
long-term, hard
endpoint

Non-drug Intervention: Staging

My experience with NP trials

Issue	Trial
Is a control group needed?	SPARX: Exercise in Parkinson's Disease
Effect of assignment ≠ effect of intervention	Surgery versus physical therapy for spinal stenosis
IRGT (what?)	Mind body intervention for low back pain
No care is "standard of care"/motivated volunteers	Physical therapy vs community center exercise program after knee replacement
No control group	Timing of surgery and rehabilitation for knee injuries

Exercise in Parkinson Disease

Courtesy of Judy Cameron, PhD, University of Pittsburgh

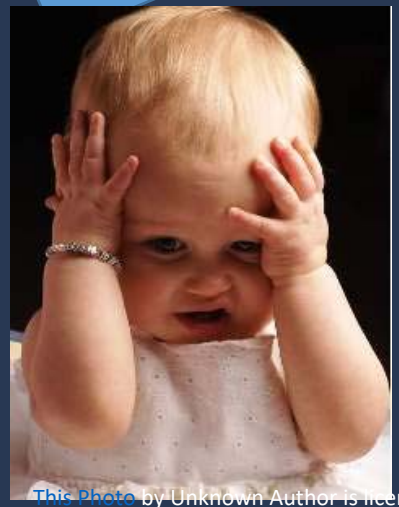
Exercise and PD

- Originally proposed
  - 2 x 2 Factorial Design
    - Intensity
    - Frequency
    - N=45 per group
    - Outcome: UPDRS motor
  - De novo PD
  - $14 M trial

Is a control group needed?

"It's just exercise."

"We do not fund small, underpowered, efficacy trials."



What we proposed: ~ Phase II

- Aim 1: Can they exercise at 65% and 80% HRmax?
- Aim 2: Does exercise warrant further investigation? (Futility Design Trial)
- Aim 3: Adverse events, attrition, feasibility in multiple sites

Concurrent Controls

Outcome/treatment group	Mean (SD)	95% CI
Primary analysis*		
Total UPDRS		
Creatine	5.6 (8.69)	(3.48, 7.72)
Minocycline	7.09 (8.71)	(4.95, 9.23)
Placebo (Calibration)	8.39 (9.76)	(6.01, 10.8)
DATATOP Placebo/Tocopherol	10.65 (10.4)	(9.63, 11.67)

- Most futility trials use historical or calibration **placebo** controls
- Placebo **drug** effect widely known in PD
- Impossible to find "natural cohort" at the time

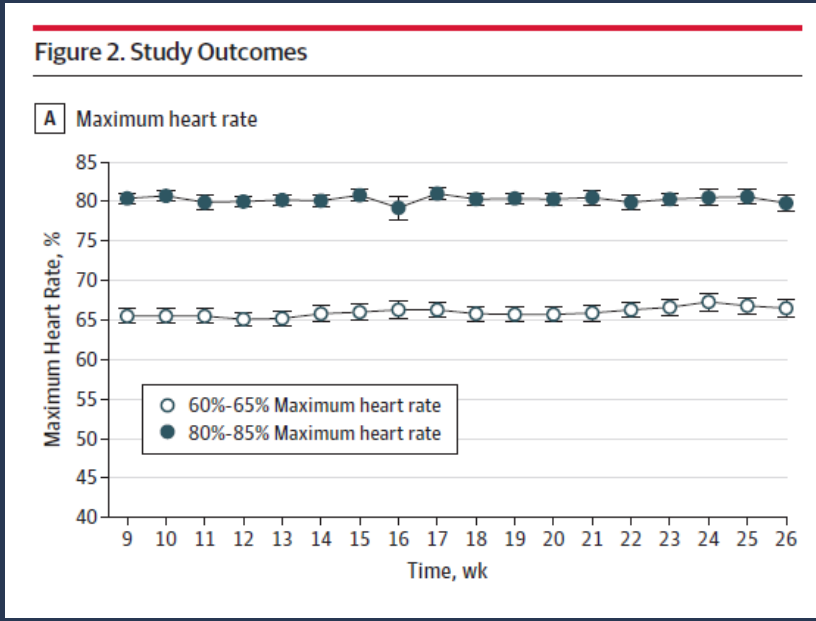
NINDS NET-PD Investigators *Neurology* 2006;66:664-671.

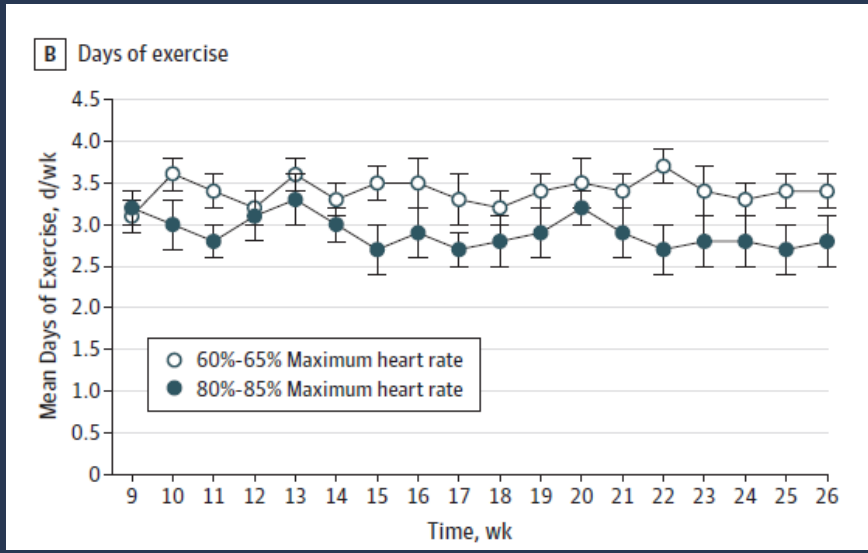
Exercise and PD

- Exercise (Aim 1)
  - 4 days per week
  - 6 months
  - 3 arms (N=126):
    - 65% HRmax
    - 80% HRmax
    - ***Usual care (waitlist)***

National Institute of Neurologic Disease and Stroke R01 NS074343

SPARX Results

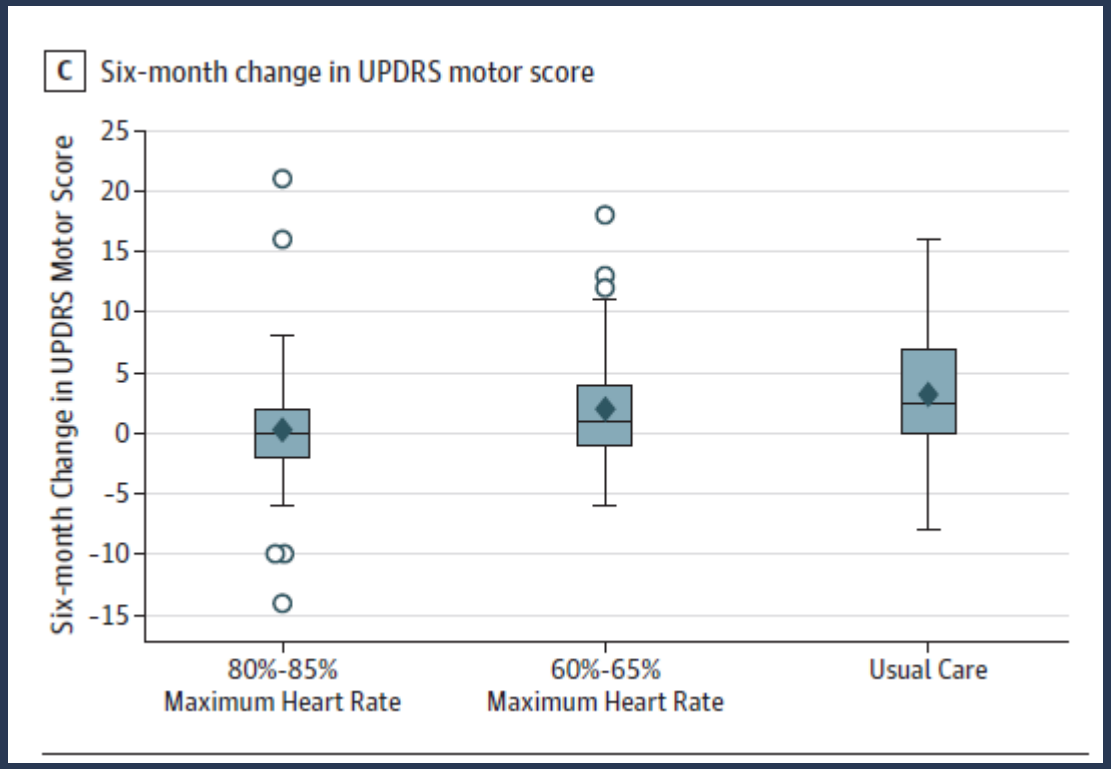




Schenkman M, **Moore CG**, Kohrt WM, Hall DA, Delitto A, Comella CL, Josbeno DA, Christiansen CL, Berman BD, Kluger BM, Melanson EL, Jain S, Robichaud JA, Poon C, Corcos DM. (2018) High-Intensity endurance exercise in Parkinson disease: A randomized, controlled Phase II trial. *JAMA Neurology* Feb 1;75(2):219-226

Table 2. Six-Month Changes From Baseline in Study Measures and Between-Group Differences in the Change from Baseline[a]

Measure	Mean (SD) [Sample Size]			Usual Care vs High-Intensity Exercise		Usual Care vs Moderate-Intensity Exercise	
	High-Intensity Exercise	Moderate-Intensity Exercise	Usual Care	Δ (CI)[b]	*t* Statistic (*P* Value)[c]	Δ (CI)[b]	*t* Statistic (*P* Value)[c]
Primary Outcome							
UPDRS motor, primary analysis[d]	0.3 (6.3) [39]	2.0 (5.3) [42]	3.2 (5.6) [38]	2.9 (<4.7)	−0.42 (.34)	1.2 (<2.8)	−1.9 (.03)
MDS-UPDRS motor[e]	0.3 (8.2)	1.8 (7.4)	4.2 (7.4)	4.0 (0.4 to 7.5)	2.21 (.03)	2.4 (−0.9 to 5.7)	1.46 (.15)



This was a Phase II – so now what?

Schenkman M, **Moore CG**, Kohrt WM, Hall DA, Delitto A, Comella CL, Josbeno DA, Christiansen CL, Berman BD, Kluger BM, Melanson EL, Jain S, Robichaud JA, Poon C, Corcos DM. (2018) High-Intensity endurance exercise in Parkinson disease: A randomized, controlled Phase II trial. *JAMA Neurology* Feb 1;75(2):219-226

Surgery vs physical therapy treatment of lumbar spinal stenosis

- To compare surgical decompression with physical therapy (PT) for lumbar spinal stenosis (LSS)

- Surgical candidates with LSS, ≥50 years
- N=169
  - 87 to surgery
  - 82 to PT
- Primary outcome: physical function @ 24 months

Delitto A, Piva SR, **Moore CG**, Fritz JM, Wisniewski SR, Josbeno DA, Fye M, Welch WC (2015). Surgery versus nonsurgical treatment for lumbar spinal stenosis: A comparative effectiveness study with 2-year follow-up. *Annals of Internal Medicine* 162(7):465-73.

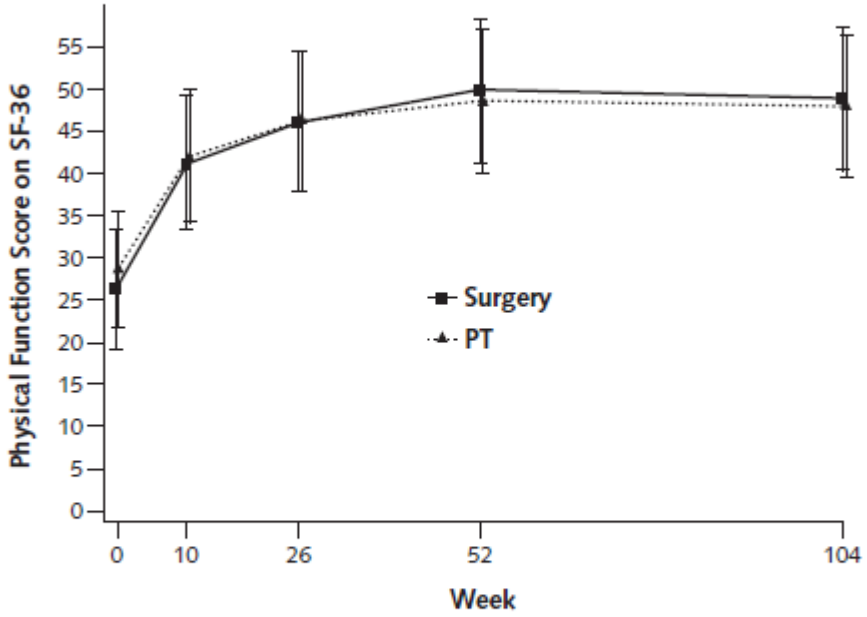
Surgery vs physical therapy treatment of lumbar spinal stenosis

- *Disclaimer: I inherited this study*
- Effect of assignment ≠ effect of intervention

- 57% of PT crossed over to surgery

Surgery vs physical therapy treatment of lumbar spinal stenosis

Figure 2. Adjusted means for physical function over time in the surgery and PT groups.



Adjusted means and 95% CIs of the physical function scale of the SF-36 for the surgery and PT groups over time from linear mixed-effects models (adjusted for sex, surgeon, and baseline age). The SF-36 scale ranges from 0 to 100, with lower scores indicating more severe symptoms. PT = physical therapy; SF-36 = Short Form-36.

- Mean improvement
  - Surgery 22.4 (95% CI, 16.9 to 27.9)
  - PT 19.2 (CI, 13.6 to 24.8)
- ITT 24-month difference
  - 0.9 [CI, −7.9 to 9.6])
- Sensitivity analyses using causal-effects methods showed no significant differences in physical function between groups.

decompression for management of patients with symptomatic lumbar spinal stenosis (LSS).

Contribution

- Patients with LSS who were surgical candidates and who provided consent for surgery were randomly assigned to physical therapy (PT) for 6 weeks or surgical decompression. Physical functioning, the primary outcome, was assessed after treatment and during the 2-year follow-up.

Caution

- Half of patients in the PT group crossed over to receive surgery.

Implication

- Patients with LSS who were offered an evidence-based PT program or surgical decompression achieved similar symptom relief and improvements in physical functioning.

Lumbar spinal stenosis (LSS) is an anatomical impairment characterized by narrowing of the spinal canal or nerve root foramen (1). When a person is

Mindfulness Meditation RCT

- To determine the effectiveness of a mind-body program in increasing function and reducing pain among older adults with chronic low back pain.

- Primary outcome: Function via Roland and Morris Disability Questionnaire

Morone NE, Greco CM, Rollman BL, Moore CG, Lane B, Morrow L, Glynn NW, Delaney J, Albert SM, Weiner DK. The Design and Methods of the Aging Succesfully with Pain Study. *Contemporary Clinical Trials*. 2012; 33:417-425. NIHMSID:338694.

National Institutes of Health 1 R01 AG034078

Design?

R A N D O M I Z E

Mindfulness Meditation

10 Keys™

Individually Randomized Group Treatment Trials

Individually Randomized Group Treatment Trials

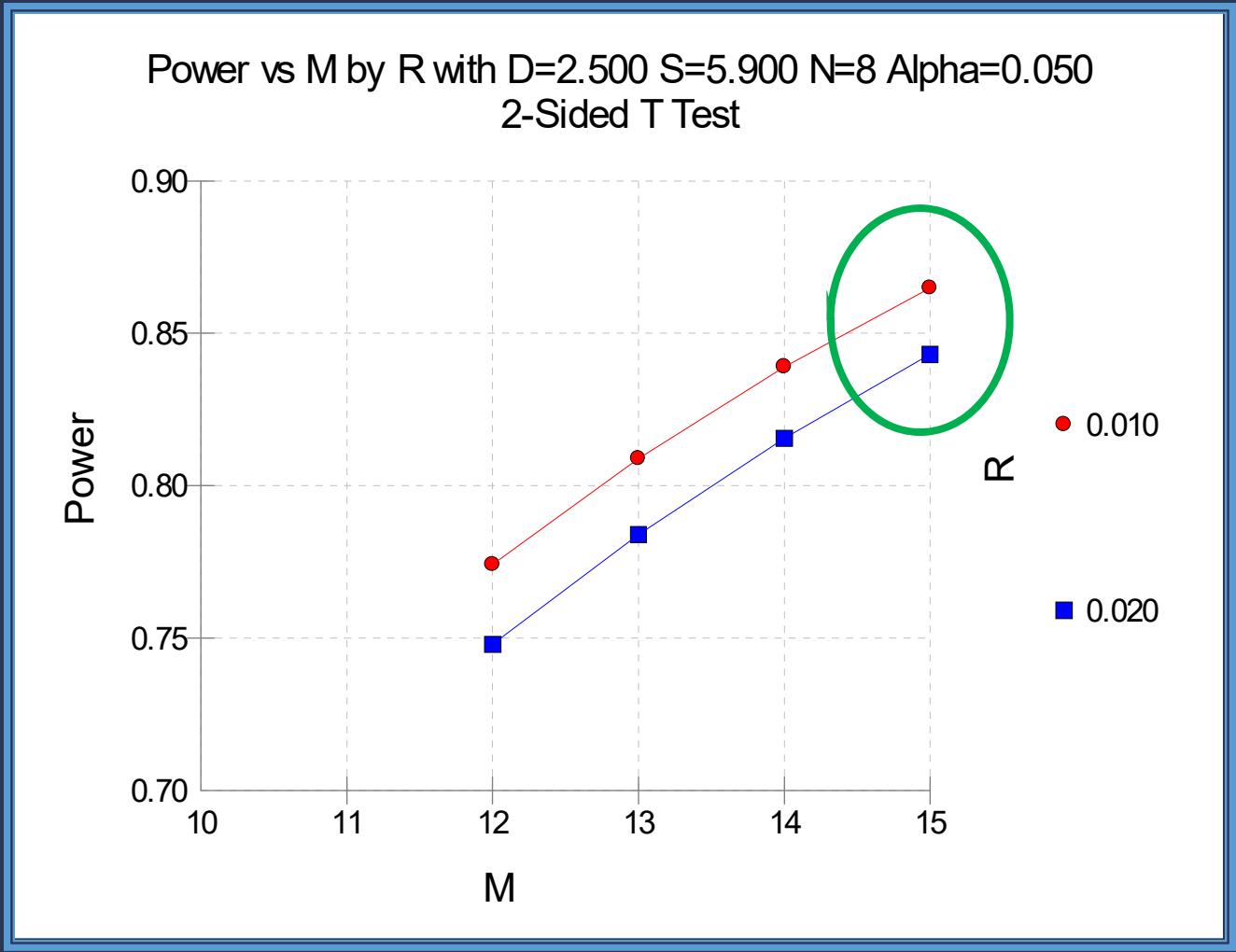
- Approximately 10 participants per class
  - Same instructor
  - Same cohort
  - Same discussions
  - Same timeframe

- What will naturally occur?

- ‘Inflate’ sample size due to clustering

$$N^* = N \times [1+(m-1)\rho]$$

$$\approx N \times (1.14) \qquad \rho=0.02,\ m=8$$



Mindfulness Meditation

"Participants attended a mean of 6.6 sessions for each group (range, 0-8 sessions)."

Table 2. Outcomes by Randomization Status[a]

Measure by Assessment	Study Group, Mean (SD) Score		Effect Size, Cohen *d* Value	Adjusted Between-Group Difference (95% CI)	*P* Value for Overall Group × Time Interaction
	Intervention (n = 140)	Control (n = 142)			
RMDQ[b]					
Baseline	15.6 (3.0)	15.4 (3.0)	NA	NA	
8-wk follow-up	12.1 (4.8)	13.1 (4.4)	−0.23	−1.1 (−2.1 to −0.01)	.01
6-mo follow-up	12.2 (5.1)	12.6 (5.0)	−0.08	−0.4 (−1.5 to 0.7)	

Remember the ICC? *ICC= 0.021*!!!

(bootstrap median, 0.016; 95% confidence limit based on 2.5% and 97.5% percentiles, 0-0.086).

Morone NE, Greco CM, **Moore CG**, Rollman BL, Lane B, Morrow LA, Glynn NW, Weiner DK. (2016) Mind-body program for older adults with chronic low back pain: A randomized controlled trial. *JAMA Internal Medicine* 2016 Mar 1;176(3):329-37

Physical therapy vs community center exercise program after knee replacement

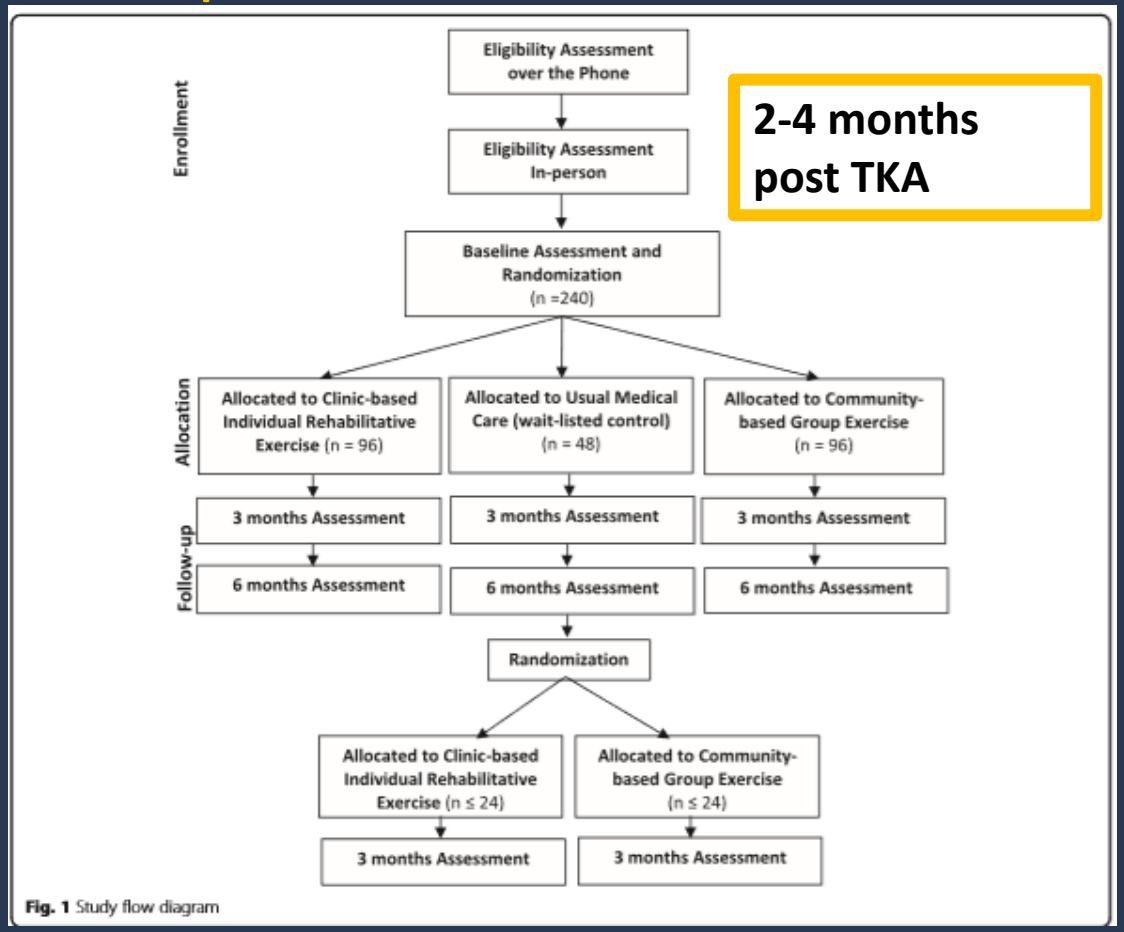


Fig. 1 Study flow diagram

2-4 months post TKA

No care is "standard of care"

Piva SR, **Moore CG**, Schneider M, Gil AB, Almeida GJ, Irrgang JJ (2015) A randomized trial to compare exercise treatment methods for patients after total knee replacement: protocol paper. *BMC Musculoskeletal Disorders* 2015 Oct 16;16:303 PCORI CER: 1310-06994

Adherence

Adherence (at 3 month)	Median (Q25, Q75)
Individual PT Sessions (n=94) (24 requested per protocol)	
Supervised PT Sessions (12 requested)	12 (12, 12)
Home Exercise Program Sessions (12 requested)	12 (12, 12)
Community PT Sessions (n=95) (24 requested per protocol)	19 (10, 24)

Co-Interventions

	PT (n=96)	Comm (n=96)	Control (n=48)	p-value
Co-Interventions				
TKR in the other knee	2 (2)	2 (2)	0 (0)	0.69
TKR revision	0 (0)	0 (0)	0 (0)	NA
THR	0 (0)	0 (0)	1 (2)	0.20
Sought HP for knee pain	16 (17)	24 (25)	8 (17)	0.29
Sought HP for pain elsewhere	31 (32)	27 (28)	14 (29)	0.81
Engaged in substantial ¥ exercise outside the study	21 (22)	18 (19)	21 (44)	0.005

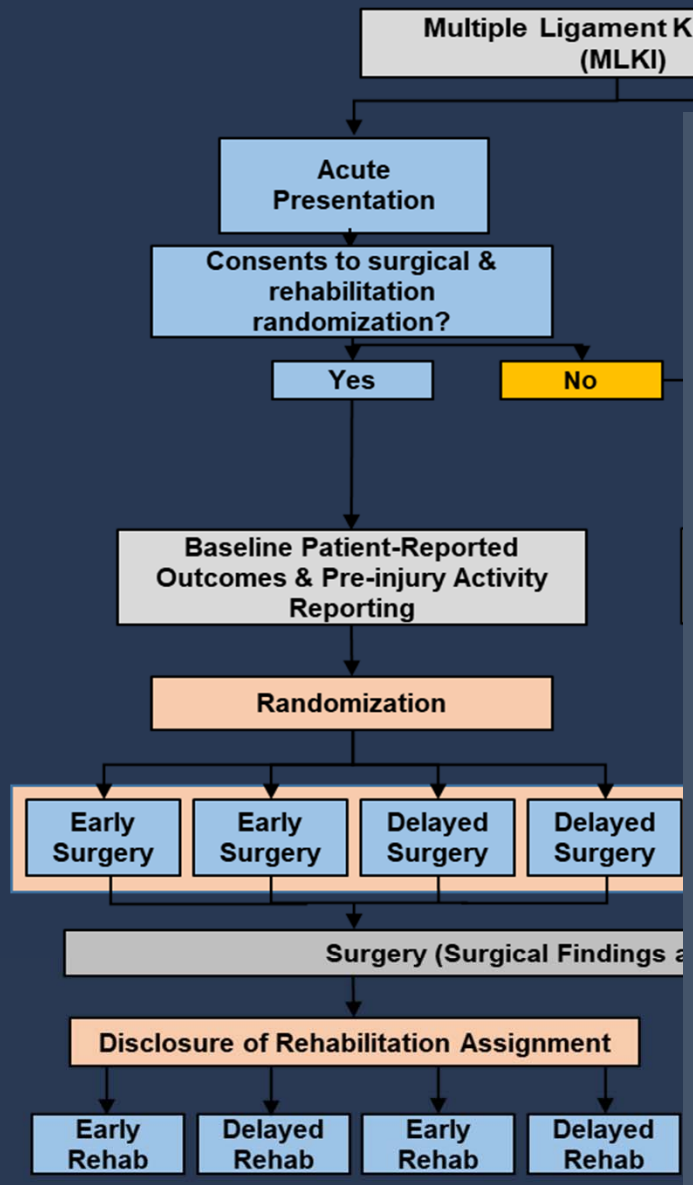
No control group

STaR TRIAL
Surgical Timing and Rehabilitation For Multiligament Knee Injury

- Multiple ligament knee injury
  - Timing of surgery (early/delayed)
  - Timing of rehabilitation (early/delayed)

"We hypothesize that early surgery, early rehabilitation and the combination of early surgery with early rehabilitation will lead to an earlier and more complete return to pre-injury military duty, work and sports and better patient-reported physical function."

	Early Surgery (<6 weeks from injury)	**Delayed Surgery (12-16 weeks from injury)** *(Control?)*
Early Rehab (WB and ROM)		
Delayed Rehab *(Control?)* **(no WB and no ROM 1 month)**		*Control?*


Multiple Ligament Knee Injury (MLKI)
Acute Presentation
Consents to surgical & rehabilitation randomization?
Yes
No
Baseline Patient-Reported Outcomes & Pre-injury Activity Reporting
Randomization
Early Surgery
Early Surgery
Delayed Surgery
Delayed Surgery
Surgery (Surgical Findings a
Disclosure of Rehabilitation Assignment
Early Rehab
Delayed Rehab
Early Rehab
Delayed Rehab

Multi-modal interventions

- Multifaceted interventions
  - “evidence appears promising for multifaceted interventions bridging the pre- and postdischarge periods”

    McWilliams A, Roberge J, **Moore CG**, Ashby A, Rossman W, Murphy S, McCall S, Brown R, Carpenter S, Rissmiller S, Furney S (2016). Aiming to improve readmissions through integrated hospital transitions (AIRTIGHT): study protocol for a randomized controlled trial. *Trials* Dec 19;17(1):603.

- At the risk of this:
  - “ it will be difficult or impossible to tease out which components are having effects.”

Summary statement from Patterson, Paul (July 2017)

Usual Care as a Control: *Do your homework!*

- Usual and unusual care: Existing practice control groups in randomized controlled trials of behavioral interventions. *Psychosomatic Medicine* 73:323-335. Freedland, Mohr, Davidson, Schwartz (2011)

- Usual care as the control group in clinical trials of nonpharmacologic interventions. *Proc Am Thorac Soc* 4:577-582. Taylor Thompson, Schoenfeld (2007)

- Considering usual medical care in clinical trial design. *PLoS Medicine* 2009 6(9):e1000111. Dawson, Zarin, et al.

- Attention placebo control in randomized controlled trials of psychosocial interventions: theory and practice. Trials 2015 16:150. Popp and Schneider

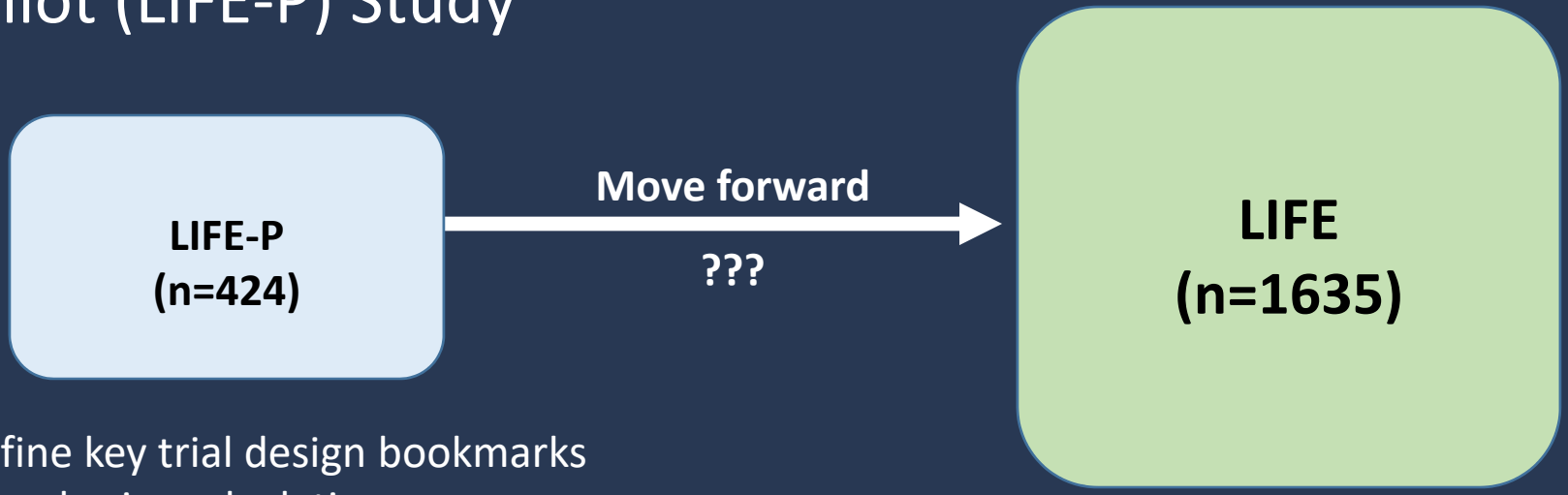
Pilot studies for NP trials

- What do you need to show before proposing a "Phase III" NP trial??

- A LOT!!!

Pilot studies for NP trials

- Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) Study

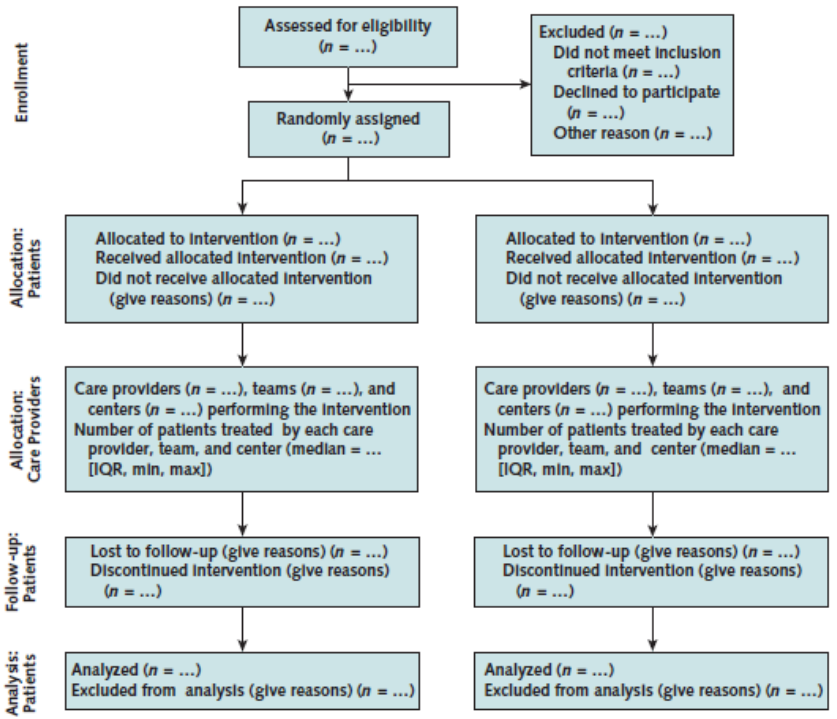


- Refine key trial design bookmarks
- Sample size calculations
- Methods for recruitment
- Participant retention
- Adherence to and safety of the interventions
- Organizational infrastructure
- Internal validity of PA: SPPB and 400-meter walk speed at 6 mo and 12 mo ➔ powered for this

1°Major mobility disability—inability to walk 400 m

CONSORT extension to NP – what is different?

Figure. Modified CONSORT flow diagram for individual randomized controlled trials of nonpharmacologic treatments.



An extra box relating to care providers and centers has been added for each intervention group. CONSORT = Consolidated Standards of Reporting Trials; IQR = interquartile range; max = maximum; min = minimum.

Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.

CONSORT (might help with protocol)

Section/ Topic Item	Checklist item no.	CONSORT Item	Extension for NPT Trials
Participants	4a	Eligibility criteria for participants	When applicable, eligibility criteria for centers and for *care providers*
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Precise **details** of both the experimental **treatment and comparator**
	5a		Description of the different **components** of the interventions and, when applicable, description of the procedure for **tailoring** the interventions to individual participants.
	5b		Details of whether and how the interventions were **standardized**.
	5c.		Details of whether and how **adherence of care providers** to the protocol was assessed or enhanced
	5d		Details of whether and how **adherence of participants** to interventions was assessed or enhanced

Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.

CONSORT (might help with protocol)

Section/ Topic Item	Checklist item no.	CONSORT Item	Extension for NPT Trials
Sample size	7a	How sample size was determined	When applicable, details of whether and how the **clustering** by care providers or centers was addressed
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	If done, who was blinded after assignment to interventions (e.g., participants, care providers**, *those administering co-interventions*,** those assessing outcomes) and how
	11c		*If blinding was not possible, description of any attempts to limit bias*

Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.

CONSORT (might help with protocol)

Section/ Topic Item	Checklist item no.	CONSORT Item	Extension for NPT Trials
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	When applicable, details of whether and how the **clustering** by care providers or centers was addressed
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	In addition, ***take into account the choice of the comparator***, lack of or partial blinding, and unequal expertise of care providers or centers in each group
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	Generalizability (external validity) of the trial findings according to the intervention, **comparators,** patients, and **care providers and centers** involved in the trial

Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.

Thank you!

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