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

Move forward

???

Pilot studies

Move forward

???

Small efficacy

Move forward

???

“Large” single center efficacy

Move forward

???

Multicenter effectiveness trial
<table>
<thead>
<tr>
<th>Issue</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a control group needed?</td>
<td>SPARX: Exercise in Parkinson’s Disease</td>
</tr>
<tr>
<td>Effect of assignment ≠ effect of intervention</td>
<td>Surgery versus physical therapy for spinal stenosis</td>
</tr>
<tr>
<td>IRGT (what?)</td>
<td>Mind body intervention for low back pain</td>
</tr>
<tr>
<td>No care is “standard of care”/motivated volunteers</td>
<td>Physical therapy vs community center exercise program after knee replacement</td>
</tr>
<tr>
<td>No control group</td>
<td>Timing of surgery and rehabilitation for knee injuries</td>
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</tbody>
</table>
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

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

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

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
This was a Phase II – so now what?

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

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

- 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.

*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.
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


National Institutes of Health 1 R01 AG034078
Design?

Mindfulness Meditation

Individually Randomized Group Treatment Trials

10 Keys™
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

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

\[ \approx N \times (1.14) \quad \rho=0.02, \quad m=8 \]
“Participants attended a mean of 6.6 sessions for each group (range, 0-8 sessions).”

<table>
<thead>
<tr>
<th>Measure by Assessment</th>
<th>Study Group, Mean (SD) Score</th>
<th>Effect Size, Cohen d Value</th>
<th>Adjusted Between-Group Difference (95% CI)</th>
<th>P Value for Overall Group &amp; Time Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention (n = 140)</td>
<td>Control (n = 142)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMDQ^a</td>
<td>15.6 (3.0)</td>
<td>15.4 (3.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Baseline</td>
<td>12.1 (4.8)</td>
<td>13.1 (4.4)</td>
<td>-0.23</td>
<td>-1.1 (-2.1 to -0.01) .01</td>
</tr>
<tr>
<td>8-wk follow-up</td>
<td>12.2 (5.1)</td>
<td>12.6 (5.0)</td>
<td>-0.08</td>
<td>-0.4 (-1.5 to 0.7)</td>
</tr>
<tr>
<td>6-mo follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Physical therapy vs community center exercise program after knee replacement

No care is “standard of care”
## Adherence

<table>
<thead>
<tr>
<th>Adherence (at 3 month)</th>
<th>Median (Q25, Q75)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual PT Sessions (n=94)</strong> (24 requested per protocol)</td>
<td></td>
</tr>
<tr>
<td>Supervised PT Sessions (12 requested)</td>
<td>12 (12, 12)</td>
</tr>
<tr>
<td>Home Exercise Program Sessions (12 requested)</td>
<td>12 (12, 12)</td>
</tr>
<tr>
<td><strong>Community PT Sessions (n=95)</strong> (24 requested per protocol)</td>
<td>19 (10, 24)</td>
</tr>
</tbody>
</table>
## Co-Interventions

<table>
<thead>
<tr>
<th>Co-Interventions</th>
<th>PT (n=96)</th>
<th>Comm (n=96)</th>
<th>Control (n=48)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TKR in the other knee</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0.69</td>
</tr>
<tr>
<td>TKR revision</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>THR</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0.20</td>
</tr>
<tr>
<td>Sought HP for knee pain</td>
<td>16 (17)</td>
<td>24 (25)</td>
<td>8 (17)</td>
<td>0.29</td>
</tr>
<tr>
<td>Sought HP for pain elsewhere</td>
<td>31 (32)</td>
<td>27 (28)</td>
<td>14 (29)</td>
<td>0.81</td>
</tr>
<tr>
<td>Engaged in substantial ￥exercise outside the study</td>
<td>21 (22)</td>
<td>18 (19)</td>
<td>21 (44)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
No control group

- 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.”

<table>
<thead>
<tr>
<th></th>
<th>Early Surgery (&lt;6 weeks from injury)</th>
<th>Delayed Surgery (12-16 weeks from injury) (Control?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Rehab (WB and ROM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed Rehab (no WB and no ROM 1 month)</td>
<td>(Control?)</td>
<td>Control?</td>
</tr>
</tbody>
</table>
Multi-modal interventions

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


• 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!*


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

- LIFE-P (n=424)
- Move forward
- LIFE (n=1635)
- 1° Major mobility disability—inability to walk 400 m

• 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
CONSORT extension to NP – what is different?

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

## CONSORT (might help with protocol)

<table>
<thead>
<tr>
<th>Section/Topic Item</th>
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<th>Extension for NPT Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>7a</td>
<td>How sample size was determined</td>
<td>When applicable, details of whether and how the <em>clustering</em> by care providers or centers was addressed</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how</td>
<td>If done, who was blinded after assignment to interventions (e.g., participants, care providers, <em>those administering co-interventions</em>, those assessing outcomes) and how</td>
</tr>
<tr>
<td></td>
<td>11c</td>
<td></td>
<td><em>If blinding was not possible, description of any attempts to limit bias</em></td>
</tr>
</tbody>
</table>

## CONSORT (might help with protocol)

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</tr>
</thead>
<tbody>
<tr>
<td>Statistical methods</td>
<td>12a</td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
<td>When applicable, details of whether and how the <strong>clustering</strong> by care providers or centers was addressed</td>
</tr>
<tr>
<td>Limitations</td>
<td>20</td>
<td>Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
<td>In addition, <em>take into account the choice of the comparator</em>, lack of or partial blinding, and unequal expertise of care providers or centers in each group</td>
</tr>
<tr>
<td>Generalizability</td>
<td>21</td>
<td>Generalizability (external validity, applicability) of the trial findings</td>
<td>Generalizability (external validity) of the trial findings according to the intervention, <strong>comparators</strong>, patients, and <strong>care providers and centers</strong> involved in the trial</td>
</tr>
</tbody>
</table>

Thank you!