What is ACCORDS?
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ACCORDS is a ‘one-stop shop’ for pragmatic research:

• A multi-disciplinary, collaborative research environment to catalyze innovative and impactful research
• Strong methodological cores and programs, led by national experts
• Consultations & team-building for grant proposals
• Mentorship, training & support for junior faculty
• Extensive educational offerings, both locally and nationally
<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Location</th>
<th>Event Title</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 10, 2024</td>
<td>10am MT</td>
<td>Zoom</td>
<td><strong>D&amp;I Science Graduate Certificate Program Informational Webinar</strong></td>
<td>Learn about the upcoming application cycle, program requirements, and key competencies.</td>
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| January 10, 2024  |          | Bushnell Auditorium, Zoom | **Ethics, Challenges, & Messy Decisions in Shared Decision Making**        | Who’s Sharing What? The Challenges of Adolescent Shared Decision Making  
**Presented by:** Ellen Lipstein, MD (Cincinnati Children’s Hospital)       |
| January 22, 2024  |          | AHSB 2200/2201, Zoom | **Statistical Methods for Pragmatic Research**                              | Missing Data and Statistical Methods                                    
**Presented by:** Jun Ying, PhD                                      |
| February 7, 2024  |          | Bushnell Auditorium, Zoom | **Ethics, Challenges, & Messy Decisions in Shared Decision Making**        | Financial Toxicity and the Importance of Cost Discussions During Shared Decision Making  
**Presented by:** Mary Politi, PhD (Washington University in St. Louis) |
| February 26, 2024 |          | Zoom              | **Statistical Methods for Pragmatic Research**                              | Latent Class Analysis: Assumptions and Extensions                        
**Presented by:** Rashelle Musci, PhD (Johns Hopkins Bloomberg School of Public Health) |

*all times 12-1pm MT unless otherwise noted*
Innovations in Pragmatic Research Methods
From Data to Equity, Policy, and Sustainability

June 5 - 7, 2024 | 10am-3pm MT

Registration is open now at www.COPRHCon.com
Factorial Designs for Optimizing Intervention Development

Maren Olsen, PhD
FACTORIAL DESIGNS FOR OPTIMIZING INTERVENTION DEVELOPMENT

Maren Olsen, PhD
Department of Biostatistics & Bioinformatics, Duke School of Medicine
ADAPT Center of Innovation, Durham VA
December 18, 2023
TODAY WE WILL TALK ABOUT …

- Motivating example: the LIFT Intervention
  - What is a factorial design? Why use a factorial design?
- Using factorial designs in Multiphase Optimization Strategy (MOST) framework
  - Goals within the framework
  - Contrast to efficacy randomized trial
  - Decision making steps
    - Analysis & sample size estimation

Acknowledgements: Dr. Chris Cox & John Gallis
THE LIFT INTERVENTION

• Intensive care unit survivors experience psychological distress post-discharge
• Mindfulness training delivered in-person has shown to improve psychological distress in various patient populations
• LIFT: adapts mindfulness training to self-directed mobile app
  • 4 weekly app-based sessions
  • Audio-guided meditation, mindfulness skills in every day life
• Pilot study: LIFT mobile-app intervention feasible & acceptable

THE LIFT INTERVENTION

• Intervention content was finalized
• However, there were additional questions about intervention delivery informed by:
  • Patient feedback → convenience & personalization
  • Staff experience → effort
  • Broader reach → Cost & scalability
• Intervention delivery options:
  LIFT Introduction
    App  Therapist Call
  Daily Dose Frequency
    Standard  High
  Elevated-Symptoms Approach
    App  Therapist Call
**FACTORIAL DESIGN**

Instead of separate trials, **efficient** way to simultaneously evaluate each intervention delivery option.

Each of the 3 components has 2 levels: \(2 \times 2 \times 2 = 8\)

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>N</th>
<th>INTRO</th>
<th>DOSE</th>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>App</td>
<td>Standard</td>
<td>App</td>
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<tr>
<td>2</td>
<td>20</td>
<td>App</td>
<td>Standard</td>
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<td>3</td>
<td>20</td>
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<td>High</td>
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<td>8</td>
<td>20</td>
<td>Call</td>
<td>High</td>
<td>Call</td>
</tr>
</tbody>
</table>

Total N = 160 participants

80 vs. 80 for levels within each component.
FACTORIAL DESIGN

- Numerous options for goals/hypotheses to be tested
- In the context of intervention development:
  - Goal: determine component levels that optimize clinical effect
  - Which components are more beneficial combined? Which are detrimental when combined?
  - Set up analyses to answer these questions

Multiphase optimization strategy (MOST) framework
MULTIPHASE OPTIMIZATION STRATEGY (MOST)

- Framework spearheaded by Dr. Linda Collins and colleagues (Collins. *Optimization of behavioral, biobehavioral, and biomedical interventions: The multiphase optimization strategy (MOST)*. Springer, 2018.)
- Using *factorial designs* to optimize interventions
- Continual optimization principle
  “Optimization is a process moving toward an ever-better intervention.”
- Resource management principle
  “An investigator using MOST must strive to make the best and most efficient use of available resources when obtaining scientific information.”

**Diagram:**
- Preparation: pilot & qualitative studies
- Optimization
- Evaluation: efficacy study
- Release Optimized Intervention
Example Hypothesis: Patients randomized to LIFT have decreased psychological distress symptoms at 1 month post-discharge compared to patients randomized to usual care.

Design and hypothesis test $\rightarrow$ clear decision
Goal: determine component levels that optimize clinical effect

Define criteria for “clinically important” effect of an intervention component

Identify important components via model estimation

Effects meeting criteria: High Level

Effects not meeting criteria: Low level

Optimized Intervention

Confirm effects via secondary outcomes, qualitative feedback, etc.
LIFT: STUDY DESIGN

- 2 x 2 x 2 factorial design
- Patients will be equally randomized to 1 of 8 groups
- Study operations look like an 8-group RCT, with assessments at baseline, 1, and 3-months

8 combinations

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>G1</td>
<td>G6</td>
<td>Call</td>
</tr>
<tr>
<td>Randomization</td>
<td>G2</td>
<td>G7</td>
<td>Call</td>
</tr>
<tr>
<td>Components</td>
<td>G3</td>
<td>G8</td>
<td>Call</td>
</tr>
<tr>
<td>Intro method</td>
<td>Call</td>
<td>Call</td>
<td>Call</td>
</tr>
<tr>
<td>Dose</td>
<td>Standard</td>
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<td>App</td>
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</table>

LIFT: DECISION-MAKING STEP 1

Define criteria for “clinically important” effect of an intervention component

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Criteria</th>
<th>Low Level</th>
<th>High Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-9 at 1 month</td>
<td>Mean difference of at least 2 points between low and high intervention component levels</td>
<td>P &lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intro Method</th>
<th>App</th>
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<tr>
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</tbody>
</table>
• Model aligned with factorial design & decision-making framework

\[ Y = \beta_0 + \beta_1 c_1 + \beta_2 c_2 + \beta_3 c_3 + \beta_4 c_1 c_2 + \beta_5 c_1 c_3 + \beta_6 c_2 c_3 + \beta_7 c_1 c_2 c_3, \]

Where \( c_1, c_2, \) and \( c_3 \) are the three intervention components

\( c_1 = \text{Intro method} \)
\( c_2 = \text{Dose} \)
\( c_3 = \text{Elevated symptoms} \)

• Effect coding (-1 vs 1) for each component. Not dummy coding (0 vs 1)

  Low level = -1 & High level = 1

Balanced design \( \rightarrow \) tests of main effects and interactions are uncorrelated
### RESULTS: EXAMINE MAIN EFFECTS AND INTERACTIONS

<table>
<thead>
<tr>
<th>Effect</th>
<th>Mean Estimate (95% CI)</th>
<th>Intro method: does not meet criteria → low level (app)</th>
<th>Dose: meets criteria → high level (high dose)</th>
<th>Elevated Symptoms: meets criteria → high level (call)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intro method main effect</strong></td>
<td>0.6 (-0.7, 1.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose main effect</strong></td>
<td>-3.8 (-5.1, -2.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Elevated symptoms main effect</strong></td>
<td>-3.0 (-4.3, -1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intro x Dose</strong></td>
<td>-0.9 (-2.2, 0.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intro x Symptoms</strong></td>
<td>5.6 (-0.1, 3.9)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Dose x Symptoms</strong></td>
<td>-4.9 (-6.3, -3.5)</td>
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<tr>
<td><strong>Intro x Dose x Symptoms</strong></td>
<td>0.5 (-0.8, 1.8)</td>
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Note: negative value indicates lower PHQ-9 (i.e., lower distress)
DOSE X SYMPTOM INTERACTION = -4.9

Plot estimated means for each level of the 2-way interaction

Synergistic interaction:
Dose = High
Elevated Symptoms = Call

→ Lowest PHQ-9 symptoms
INTRO X SYMPTOM INTERACTION = 5.6

- Plot estimated means for each level of the 2-way interaction

Antagonistic interaction:
Intro = Call
Elevated Symptoms = Call

→ Increased PHQ-9 symptoms
LIFT: OPTIMIZED INTERVENTION

Identify important components via model estimation

Effects meeting criteria: **High Level**

Effects not meeting criteria: **Low level**

Confirm effects via secondary outcomes, qualitative feedback, etc.

Optimized Intervention

<table>
<thead>
<tr>
<th>Intro Method</th>
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Optimized Intervention
LIFT: NEXT STEP
MOST FRAMEWORK

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Preparation: pilot & qualitative studies

Optimization

Evaluation: efficacy study

Release Optimized Intervention
Revisit model …

\[ Y = \beta_0 + \beta_1 c1 + \beta_2 c2 + \beta_3 c3 + \beta_4 c1c2 + \beta_5 c1c3 + \beta_6 c2c3 + \beta_7 c1c2c3, \]

Where \( c1, c2, \) and \( c3 \) are the three intervention components

- Effect coding \((-1 \text{ vs } 1)\) for each component
- Effects are independent

**Hypothesis test of interest**: Detect the mean difference between levels of main effect

\[
ME_k = \mu_{c_k=+1} - \mu_{c_k=-1} \\
= +1 \beta_k - (-1 \beta_k) \\
= 2\beta_k
\]
• Calculations via two-sample t-test
• Sample size in each group = \# randomized to receive each level of main effect

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Total N = 160 participants
80 vs. 80 for a main effect comparison
**Continuous outcomes:**

SAS macro:

https://scholarsphere.psu.edu/resources/4c3ff64a-f92e-41d7-924e-b158fb5014f9

R package: MOST

https://cran.r-project.org/web/packages/MOST/MOST.pdf

Options include:

- Pre-post correlation
- Clustered design, with ICC


**Empirical power via simulation** for more complicated designs:

- Clustered, non-continuous outcomes
- Longitudinal data (≥ 3 time points)
ADDITIONAL EXAMPLES

  • 3 factors ($2^3 = 8$ experimental conditions), primary outcome = physical activity at 16 weeks
  • Includes discussion of all MOST-framework phases, results, and challenges

  • 5 factors ($2^5 = 32$ experimental conditions), primary outcome = weight loss from baseline to 6 months
  • Decision-making process includes higher-order interactions & per-person costs
• MOST provides framework for decision-making process
  • Different objective than RCT for efficacy
  • Instead, RCT with factorial design to optimize levels of intervention components
• Other considerations --- costs, feasibility, stakeholder feedback
• Ongoing area of research:
• Challenges:
  • Funding possibilities?
  • Communication/publication of findings? (Note: CONSORT guidelines for factorial designs)