What is ACCORDS?

Adult and Child Center for Outcomes Research and Delivery Science

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

ACCORDS Upcoming Events

January 10, 2024 10am MT Zoom	**D&I Science Graduate Certificate Program Informational Webinar** Learn about the upcoming application cycle, program requirements, and key competencies.
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

COPRH Con

Colorado Pragmatic Research in Health Conference

Innovations in Pragmatic Research Methods

From Data to Equity, Policy, and Sustainability

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

ACCORDS

ADULT AND CHILD CENTER FOR OUTCOMES RESEARCH AND DELIVERY SCIENCE

UNIVERSITY OF COLORADO
CHILDREN'S HOSPITAL COLORADO

Registration is open now at www.COPRHCon.com

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Statistical Methods for Pragmatic Research Seminar Series

2023-2024 seminar series

Maren Olsen, PhD

Factorial Designs for Optimizing Intervention Development

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

Cox CE, et al. Effects of mindfulness training programmes delivered by a self-directed mobile app and by telephone compared with an education programme for survivors of critical illness: a pilot randomized clinical trial. *Thorax* 74.1 (2019): 33-42.

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 x 2 x 2 = 8

Experimental Condition	N	INTRO	DOSE	SYMPTOMS
1	20	App	Standard	App
2	20	App	Standard	Call
3	20	App	High	App
4	20	App	High	Call
5	20	Call	Standard	App
6	20	Call	Standard	Call
7	20	Call	High	App
8	20	Call	High	Call

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

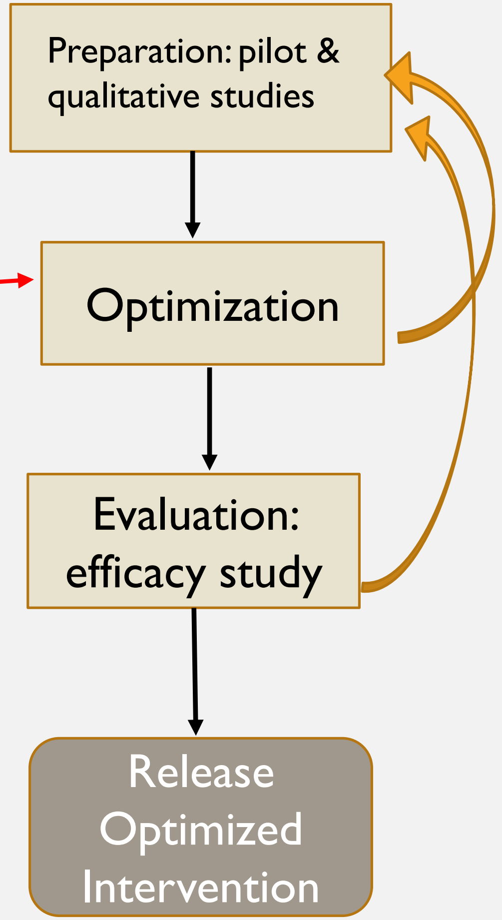
→ Multiphase optimization strategy (MOST) framework

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

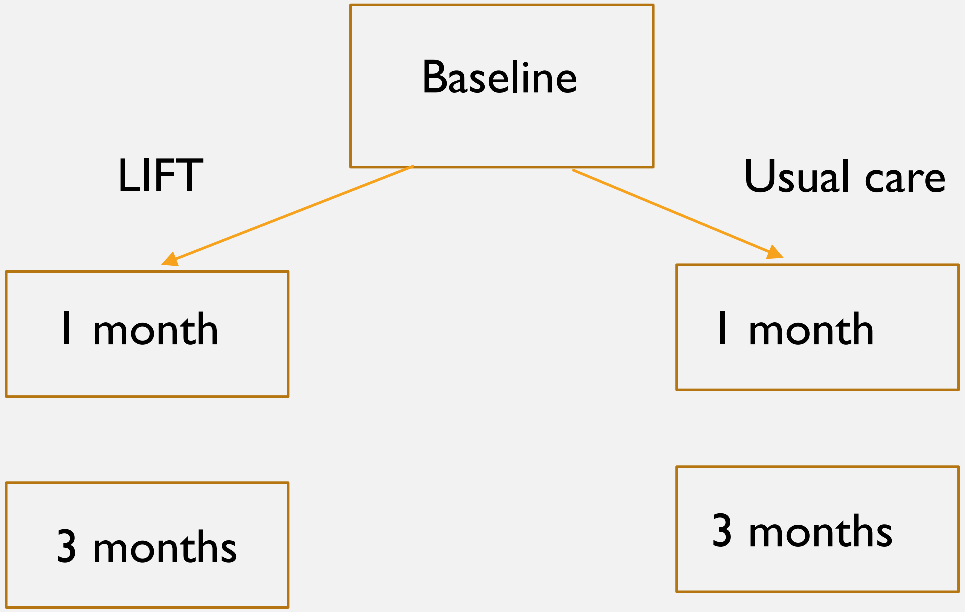
  "Optimization is a process moving toward an ever-better intervention."
- Resource management principle

  "An investigator using MOST must strive to make the best and most efficient use of available resources when obtaining scientific information."



EFFICACY TRIAL: DECISION MAKING

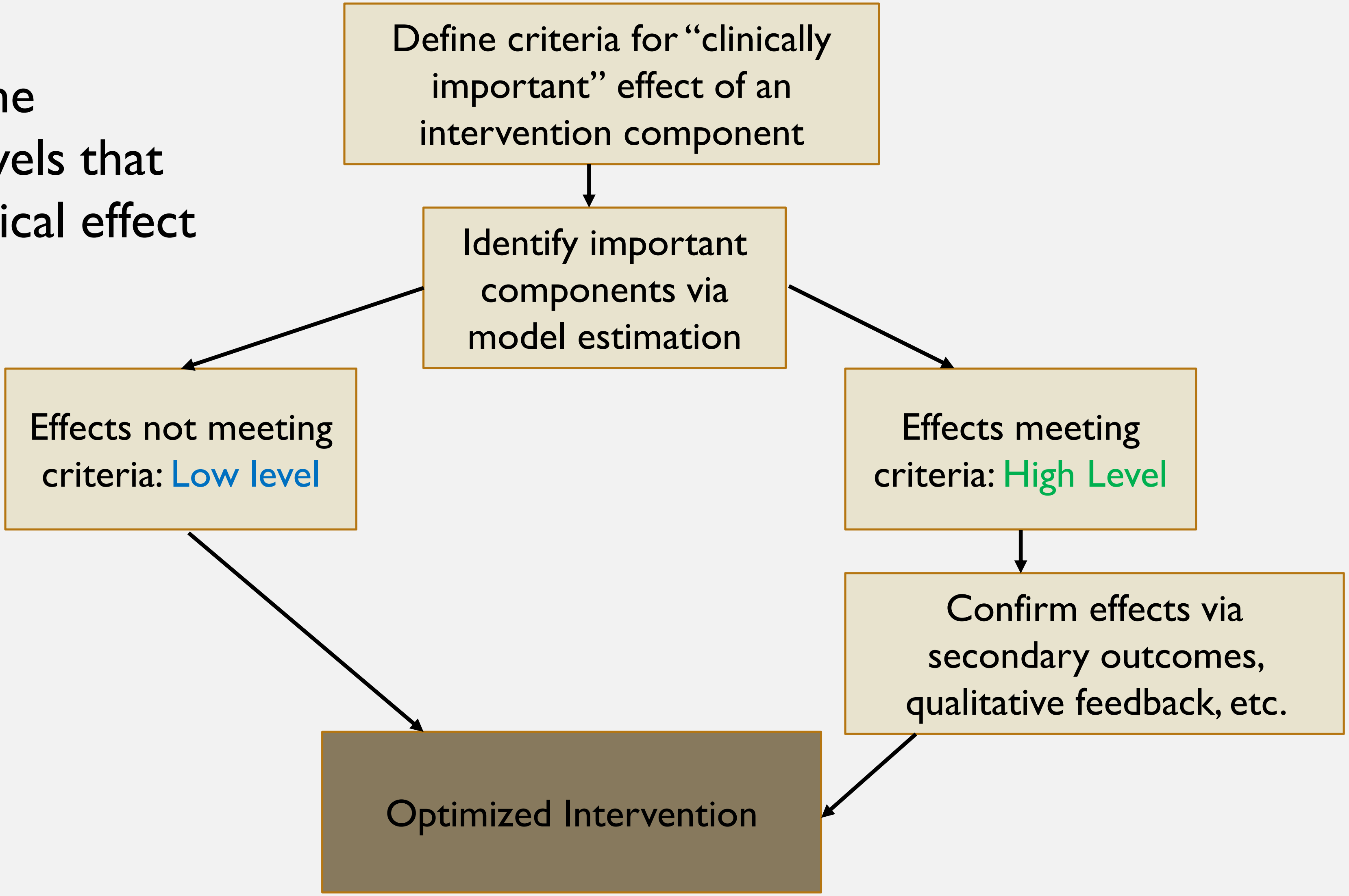
Example Hypothesis: Patients randomized to LIFT have decreased psychological distress symptoms at 1 month post-discharge compared to patients randomized to usual care



Design and hypothesis test → clear decision

MOST FRAMEWORK: GENERAL DECISION-MAKING PROCESS

★ Goal: determine component levels that **optimize** clinical effect



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

Enrollment	T1	Randomization	Components	G1	G2	G3	G4	G5	G6	G7	G8	T2	T3
	Baseline		Intro method	App	App	App	App	Call	Call	Call	Call	1-month assessment	3-month assessment
			Dose	Standard	Standard	High	High	Standard	Standard	High	High		
			Elevated symptoms	App	Call	App	Call	App	Call	App	Call		

Cox CE, et al. Optimizing a self-directed mobile mindfulness intervention for improving cardiorespiratory failure survivors' psychological distress (LIFT2): Design and rationale of a randomized factorial experimental clinical trial. Contemp Clin Trials. 2020 Sep;96:106119. PMCID: PMC7428440.

LIFT: DECISION-MAKING STEP 1

Define criteria for "clinically important" effect of an intervention component

Primary Outcome	Criteria	
PHQ-9 at 1 month	Mean difference of at least 2 points between low and high intervention component levels	$P < 0.05$

	Low Level	High Level
Intro Method	App	Call
Dose	Standard	High
Elevated symptoms	App	Call

LIFT: DECISION MAKING STEP 2

Identify important components via model estimation

- Model aligned with factorial design & decision-making framework

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

Where $c1, c2,$ and $c3$ are the three intervention components

$c1$ = Intro method

$c2$ = Dose

$c3$ = Elevated symptoms

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

  Low level = -1 & High level = 1

Balanced design → tests of main effects and interactions are uncorrelated

RESULTS: EXAMINE MAIN EFFECTS AND INTERACTIONS

Effect	Mean Estimate (95% CI)
Intro method main effect (c_1)	0.6 (-0.7, 1.9)
Dose main effect (c_2)	**-3.8 (-5.1, -2.5)**
Elevated symptoms main effect (c_3)	**-3.0 (-4.3, -1.6)**
Intro x Dose (c_1c_2)	-0.9 (-2.2, 0.4)
Intro x Symptoms (c_1c_3)	**5.6 (-0.1, 3.9)**
Dose x Symptoms (c_2c_3)	**-4.9 (-6.3, -3.5)**
Intro x Dose x Symptoms ($c_1c_2c_3$)	0.5 (-0.8, 1.8)

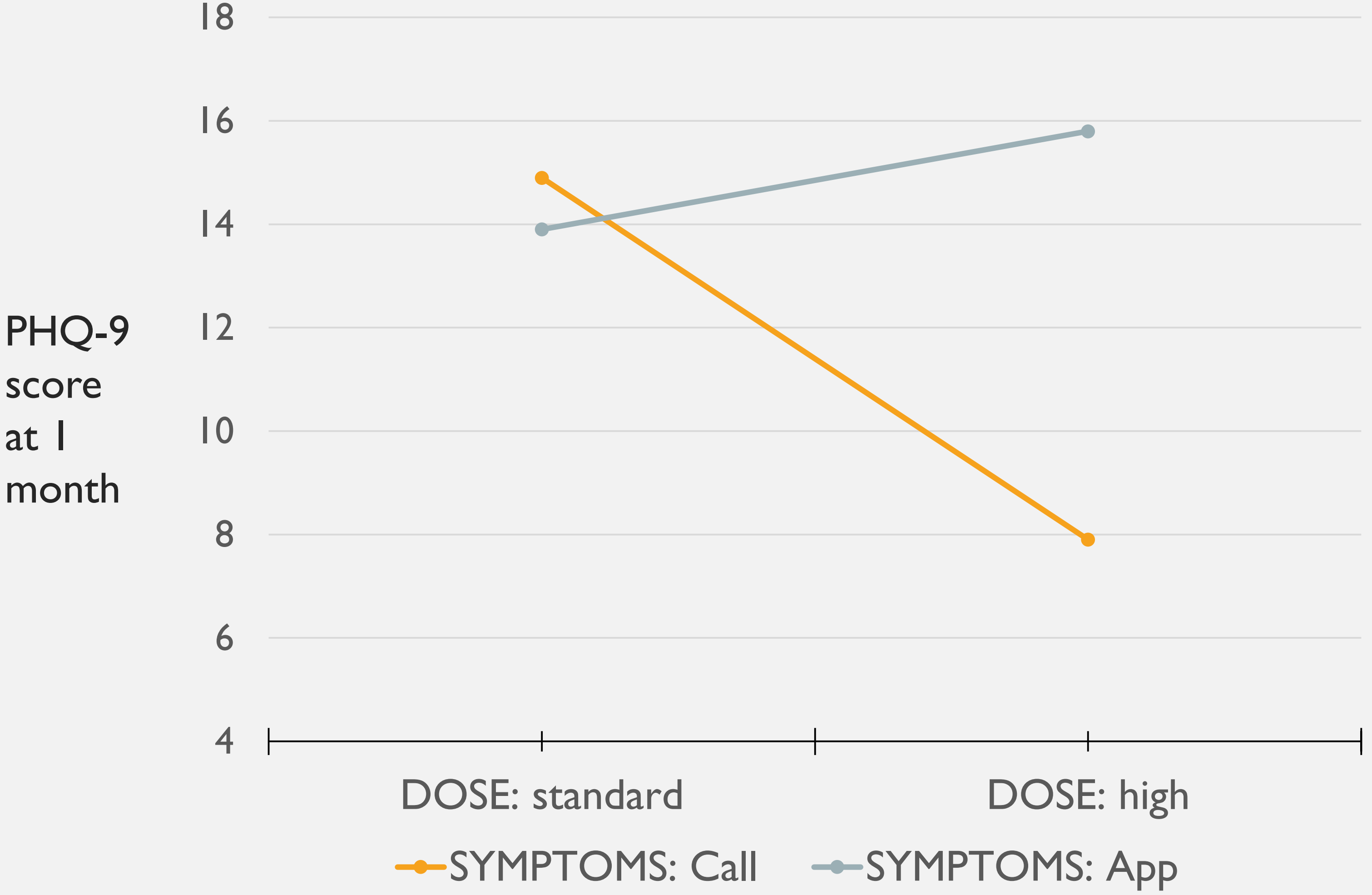
Note: negative value indicates lower PHQ-9 (i.e., lower distress)

Intro method: does not meet criteria → low level (app)

Dose: meets criteria → high level (high dose)

Elevated Symptoms: meets criteria → high level (call)

DOSE X SYMPTOM INTERACTION = -4.9

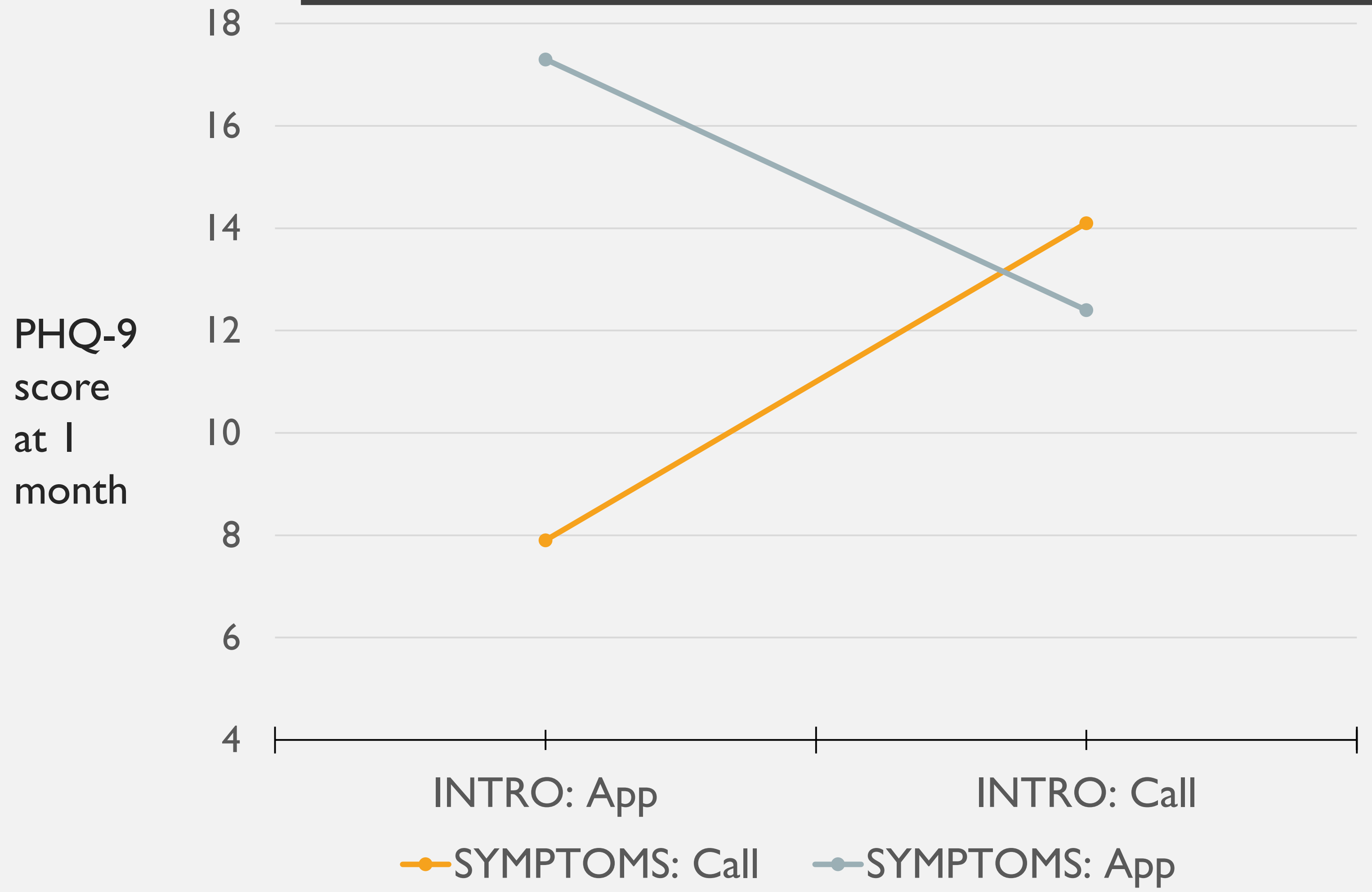


- Plot estimated means for each level of the 2-way interaction

Synergistic interaction:
Dose = High
Elevated Symptoms = Call

→ Lowest PHQ-9 symptoms

INTRO X SYMPTOM INTERACTION = 5.6

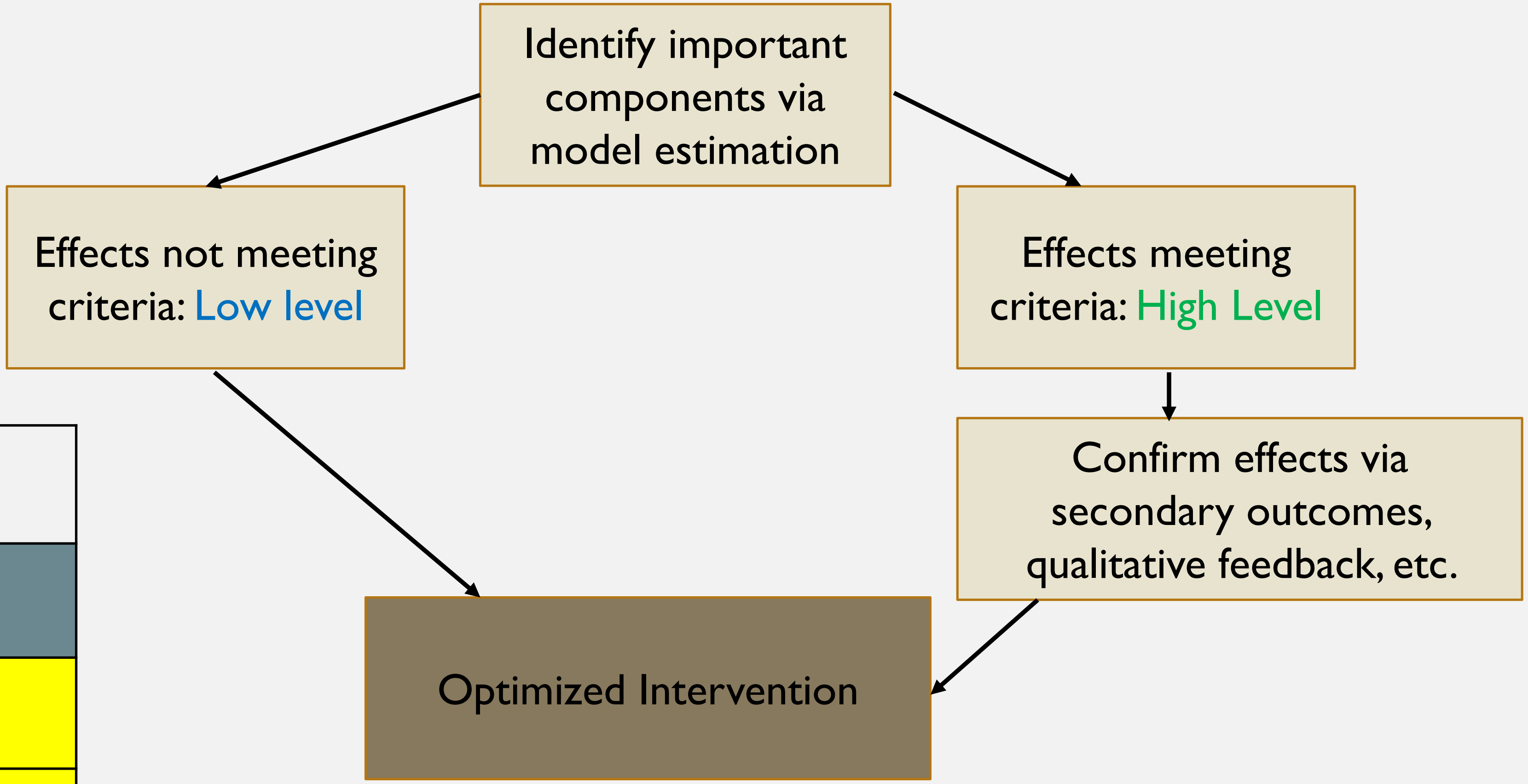


- Plot estimated means for each level of the 2-way interaction

Antagonistic interaction:
Intro = Call
Elevated Symptoms = Call

→ Increased PHQ-9 symptoms

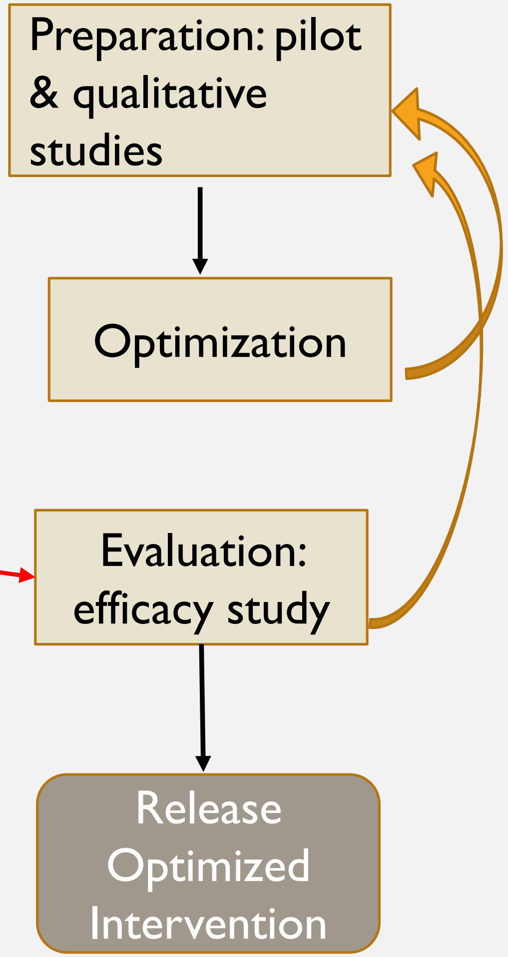
LIFT: OPTIMIZED INTERVENTION



	Low Level	**High Level**
Intro Method	App	Call
Dose	Standard	High
Elevated symptoms	App	Call

LIFT: NEXT STEP
MOST FRAMEWORK

	Low Level	High Level
Intro Method	App	Call
Dose	Standard	High
Elevated symptoms	App	Call



MOST: SAMPLE SIZE CONSIDERATIONS

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 vs 1) for each component
- Effects are independent

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

$$ME_k = \mu_{ck=+1} - \mu_{ck=-1}$$

$$= +1\,\beta_k - (-1\,\beta_k)$$

$$= 2\beta_k$$

MAIN EFFECT MEAN DIFFERENCE

- Calculations via two-sample t-test
- Sample size in each group = # randomized to receive each level of main effect

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7	20	Call	High	App
8	20	Call	High	Call

Total N = 160 participants

80 vs. 80 for a main effect comparison

MOST-SPECIFIC SOFTWARE OPTIONS

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

Group-based designs: Nahum-Shani, Inbal, John J. Dziak, and Linda M. Collins. "Multilevel factorial designs with experiment-induced clustering." *Psychological methods* 23.3 (2018): 458.

Empirical power via simulation for more complicated designs:

- Clustered, non-continuous outcomes
- Longitudinal data ($\geq$ 3 time points)

ADDITIONAL EXAMPLES

- Huffman, J. C., et al (2019). Developing a Psychological–Behavioral Intervention in Cardiac Patients Using the Multiphase Optimization Strategy: Lessons Learned From the Field. *Annals of Behavioral Medicine*.
  - 3 factors (2^3 = 8 experimental conditions), primary outcome = physical activity at 16 weeks
  - Includes discussion of all MOST-framework phases, results, and challenges
- Spring, Bonnie, et al. "A factorial experiment to optimize remotely delivered behavioral treatment for obesity: results of the Opt-IN study." *Obesity* 28.9 (2020): 1652-1662.
  - 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

WRAP-UP

- 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:
  - Discussion in this paper: Linda M Collins, Jillian C Strayhorn, David J Vanness, One view of the next decade of research on behavioral and biobehavioral approaches to cancer prevention and control: intervention optimization, *Translational Behavioral Medicine*, Volume 11, Issue 11, November 2021, Pages 1998–2008.
  - Strayhorn, J. C., Cleland, C. M., Vanness, D. J., Wilton, L., Gwadz, M., & Collins, L. M. (2023, August 3). Using Decision Analysis for Intervention Value Efficiency to Select Optimized Interventions in the Multiphase Optimization Strategy. Health Psychology. Advance online publication. https://dx.doi.org/10.1037/hea0001318
- Challenges:
  - Funding possibilities?
  - Communication/publication of findings? (Note: CONSORT guidelines for factorial designs)