SAVANNAH CONVENTION CENTER // SAVANNAH, GEORGIA, USA

SIO 2026

Annual Scientific Meeting

4-8 FEBRUARY

Statistical Considerations for IO-Specific Trial Designs

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2026 Annual Scientific Meeting

Disclosures

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- Salary support from Merck (~5%), paid directly to Penn, 2024-2026

IO interventions are complex.

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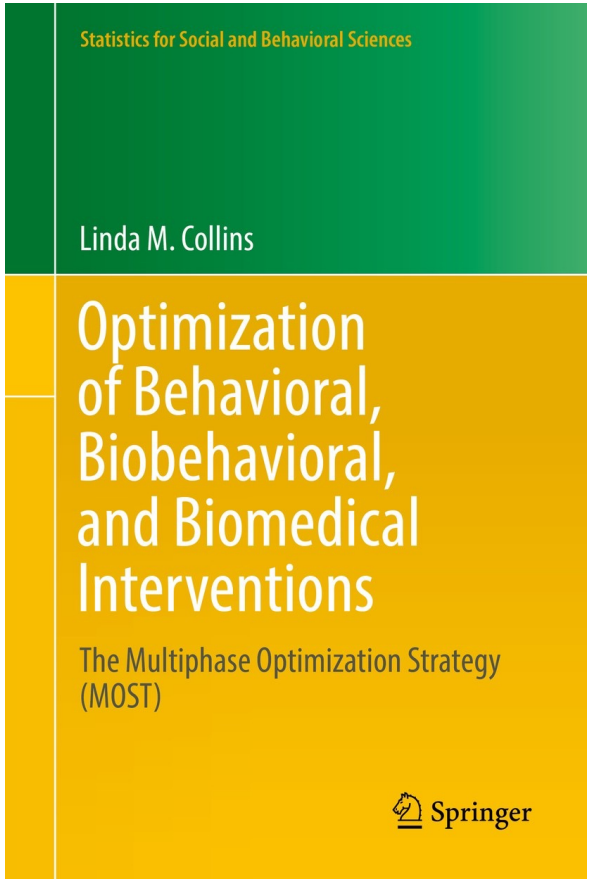
- Studying complex interventions requires **very** careful thought.
- Challenges can be mitigated with **high-quality design**.
  - Design of both the intervention *and* a trial.
- Well-designed interventions and studies make statistical analysis straightforward, *depending on the objective*.
  - Poor design makes it hard to achieve high-quality results ☹️

Plug: The Multiphase Optimization STrategy (MOST)

- **MOST** is a framework for developing and optimizing multicomponent or multiphase interventions
- Often used in behavioral or biobehavioral settings, but applicable in biomedical applications as well.
- *Preparation phase* develops a conceptual model for the intervention's mechanism.
- *Optimization phase* uses experimentation (RCTs) to identify effective components, delivery strategies, etc.
- *Evaluation phase* studies the effects of the optimized intervention.



Objectives, Endpoints, and Estimands

- A trial's **objective** is the scientific question of interest
  - "Is [intervention A] [superior to] [intervention B] in terms of [endpoint]?"
- An **endpoint** is the outcome measure for an *individual patient*.
  - PFS, OS, objective response (not response *rate*), etc.
  - Not estimated, *measured*.
- An **estimand** is a population-level quantity of interest that addresses the scientific question
  - Difference in ORR, median survival, etc.
  - Translates the objective to a statistical target quantity.
  - Estimated.

Some obvious points worth repeating:

- In a clinical trial,
- You can only study what you *do*.
- You can only compare what you *vary*.
- You can only *easily* compare what you *randomize*.

- ***Clearly establishing and justifying your primary scientific question is crucial.***

Establishing a Scientific Question

- Your trial is designed to answer specific scientific questions (objectives)
- Objectives must be **clear and explicit.**
- This is especially true for trials of complex interventions!

- Your scientific question should be about *one or more interventions* as they relate to some outcome/endpoint of interest.

- If investigating a multicomponent intervention, do you want to evaluate *each component* or the *entire package*?

Defining the Intervention

- Having **clearly defined, protocolized interventions** is crucial.
- What does this mean?
- Dose
  - For drugs *and* procedures: How much *stuff* are you delivering?
- Timing
  - When is the *stuff* being delivered?
    - Continuously? At pre-defined intervals? Trigger-based?

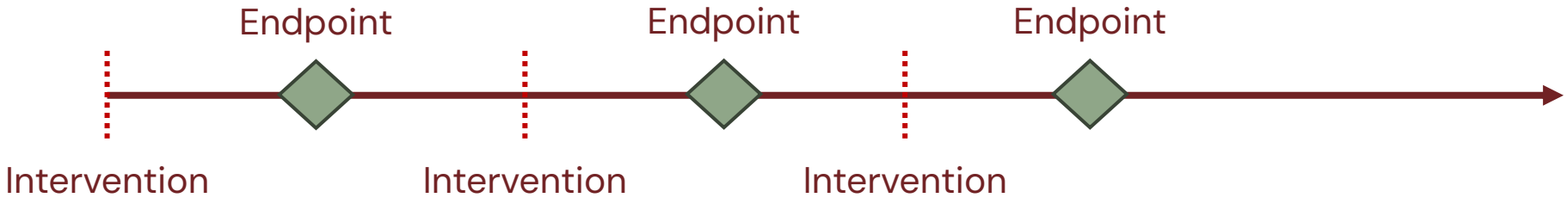
Defining the Intervention

- Having **clearly defined, protocolized interventions** is crucial.
- What does this mean?
- Duration
  - How long does the intervention last or take to be delivered?
  - E.g., how long between procedures, drug administrations, etc.?
- Minimum required components / compliance / adherence
  - What does a patient need to have received to have “complied” with the intervention?

Endpoint Timing and Measurement

- ”Time scale” of endpoints should match the scientific question and the intervention as defined.

- If the scientific question is about a single procedure, dose, etc., the endpoint should be **proximal** (near in time to treatment delivery).

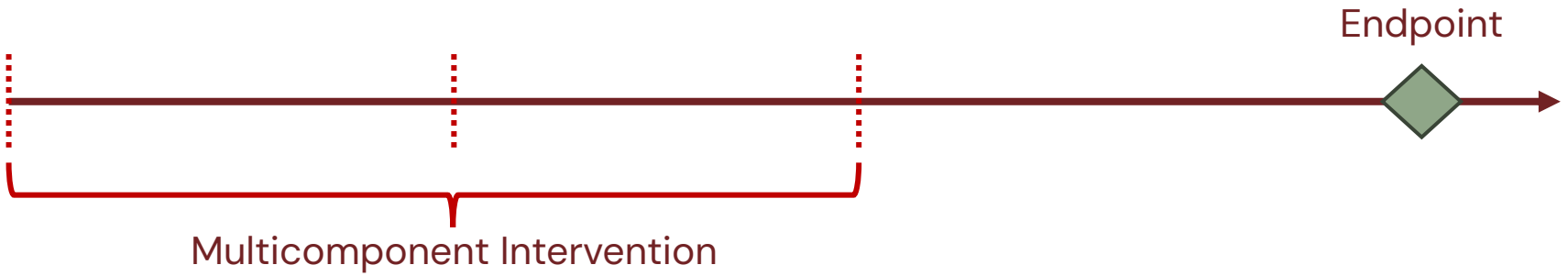


- This yields repeated measures on the same patient.

Endpoint Timing and Measurement

- ”Time scale” of endpoints should match the scientific question and the intervention as defined.

- If the endpoint is **distal** (far in time from treatment delivery), you may need to reconceptualize the intervention:



- We can only study the effects of all intervention components *jointly*.

Why does this matter?

- If delivering multiple treatments, and your question is about a single administration, the endpoint must be observable before the next administration.
- Otherwise, the endpoint could be affected by subsequent administrations, leading to a biased treatment effect estimate.
- Unpacking each administration's effect would complex statistical techniques.
- MOST is useful in this setting if interested in optimization.

Efficacy vs. Effectiveness

- **Efficacy** is how well something works in ideal settings (e.g., the lab)
  - Requires clear protocolization (of both treatment and control)
- **Effectiveness** is how well something works in the real world
  - Allows flexibility in implementation, clinical judgment, etc.

- Be very explicit about what in your intervention needs to be protocolized and what's allowed to vary (and *how*).

Time-to-event endpoints with staged or multicomponent interventions

- It's important to define endpoints to avoid **immortal time bias**
- Clocks should start with the intervention, *not* when the intervention is "complete"
  - If randomizing, clocks should start at randomization.
- Example: trial of continuous drug vs. staged embolization
  - If PFS starts after last embolization, the continuous drug arm has already had time for progressions to occur (BIAS!)

Get a biostatistician involved ASAP!

Scan for slides:

- **Involve us as early as possible!**
- We can help with:
  - Clarifying objectives, hypotheses, and endpoints
  - Trial design
  - Analytic strategies to improve efficiency
  - Improving trial data collection and quality
  - And much more!
- We’re more than a checkbox or a power calculation.
- You know more about IO than we do, but we learn fast.
  - Outside knowledge can be helpful: we’re good at asking “why?”