Designing Trials within Implementation Laboratories Sequential Multiple-Assignment Randomized Trials

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Presentation roadmap

- Adaptive interventions & SMART designs in implementation research: The rationale
- **Example:** Using facilitation to hasten uptake of a collaborative care model in an implementation laboratory
- Strengths & challenges of SMART designs in implementation research & for implementation laboratories

ADAPTIVE INTERVENTIONS & SMART DESIGNS in implementation research

Some definitions

An adaptive intervention (Al) is an intervention design where: intervention options are adapted to accommodate specific & changing needs of participants to provide sequences of treatments.

SMARTs are <u>multi-stage randomized trials</u> designed to inform the construction of effective **adaptive interventions**.

Als in implementation research

For implementation scientists, SMARTs offer chance to explore **sequences of implementation support**

Adaptive implementation interventions



Als in implementation research

Often insufficient evidence/theory to decide:

- Which strategy(ies) should I *start with*?
- What should I do for sites that are *non-responsive* to first-line treatment?
- What should I do for sites that are *responsive* to first-line treatment?

SMART studies

can help to answer these questions.

EXAMPLE: Determining optimal facilitation support



The question:

What is the **best way** to implement a collaborative care model (CCM) in **community-based mental health centers**?

Implementation strategy options

REP

(Replicating Effective Programs) Provides intervention manualization, didactic training and technical assistance. (External facilitation) Help identifying & addressing barriers from an outside 'expert.'

EF

IF al facilit

(Internal facilitation) Inside expert who works with site leaders to address barriers & champion cause.

Less intensive

More intensive

Prior evidence says:

REP will work for some sites

- But we don't *really* know which...

Most sites will need more support than REP

But we don't know:

- What do we do when **REP doesn't work**?
 - Step up directly to EF/IF or to EF?
 - What if we step up to EF but sites still don't respond?

Study goal:

Develop the **best adaptive sequence of implementation interventions (REP, EF, EF/IF)** for improving patient mental health by encouraging uptake of CCM in community-based practices.

Design:

Three-phase clustered (patients in sites) SMART















Questions we can answer

Example Aim 1:

Determine among patients in sites that do not exhibit response to REP alone, the <u>effect of adding an</u> <u>External and Internal Facilitator (REP + EF/IF)</u> versus <u>REP + EF</u> on patient-level changes in mental health-related quality of life (MH-QOL) <u>month 6 to month</u> <u>18</u>.



Questions we can answer

Example Aim 2:

Determine, among <u>REP + EF sites</u> that continue to exhibit non-response after an additional 6 months, the effect of continuing <u>REP + EF</u> vs. <u>REP + EF/IF</u> on patient-level changes in the primary outcome from <u>month 12 to month 18</u>.



Questions we can answer

Compare embedded Als:



Questions we can answer

Compare embedded Als:







Questions we can answer

Moderators (e.g.):

- Do patients at **larger sites** <u>benefit more</u> from initial assignment to EF/IF than EF?
- Do patients at sites initially randomized to EF that **narrowly missed the response cut-off** <u>benefit more</u> from continuing EF than stepping up to EF/IF?

STRENGTHS & CHALLENGES of SMART designs in implementation laboratories

Strengths

- Implementation comparative effectiveness
 research
 - Leverage large numbers of sites/providers/patients for more nuanced implementation inquiries
 - Everyone (can) get something beyond usual care
 - Less waste (Ivers & Grimshaw, 2016)
- Hybrid implementation-effectiveness designs allow for consideration of both proximal & distal outcomes
 - Did they do it? & did it work?

Strengths

- Robust design allows for causal inference
- Compared to **single-stage trials**:
 - Better detection of delayed effects
 - Better protection against selection effects
 - Better retention for non-responding sites

Strengths

- Moderators (including <u>time-varying</u>) can inform more deeply-tailored Als
 - Inform efforts to understand, model & leverage learning health care systems for improved health care delivery
 - "Precision implementation" efforts

Challenges

- SMARTs are not adaptive trial designs
 - Inform an understanding of how to adapt delivery of implementation strategies, but study design itself do not adapt
- Need to make informed decisions up front about which strategies to use & when, decision points, tailoring variables, etc.

Challenges

- Alignment of decision points across
 multiple (many!) sites
- Ensure that data are captured at timescales necessary for evaluations of interest (e.g., moderators) for all sites

Challenges

- Requires protocols & adherence to protocols for varying levels of data collection (sites, providers, patients)
- Some methods for clustered SMARTs are still in development
- No classic evaluation of "best" adaptive implementation intervention

SMART Resources & References

ADEPT protocol paper:

Kilbourne, A. M. et al. (2014). Implementation Science, 9(1), 132.

Penn State Methodology Center SMART examples:

https://methodology.psu.edu/ra/adap-inter/projects

SMART sample size calculations:

- Continuous outcomes: Oetting, A. I., et al (2011). Causality and psychopathology: finding the determinants of disorders and their cures, pp. 179-205.
- *Binary outcomes:* Kidwell, K. M., et al (2017). Journal of Applied Statistics, 1-24.
- *Cluster-randomized:* NeCamp, T., Kilbourne, A., & Almirall, D. (2017). Statistical Methods in Medical Research, 26(4), 1572-1589.

SMART Questions?

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Extra slides

SMARTs are multi-stage randomized trials designed to inform the construction of effective **adaptive interventions**.

An **adaptive intervention (AI)** is an intervention design where:

- intervention options are adapted to accommodate specific & changing needs of participants (individuals, sites)
- to provide **sequences** of individualized treatments.

Treatment start:

Provide implementation strategy A for all sites

After 3 months:

If site is a <u>responder</u>:

Then, strategy ={low-level monitoring}

If site is a <u>non-responder</u>:



Treatment start:

Provide implementation strategy A for



After 3 months:

If site is a <u>responder</u>:

Then, strategy ={low-level monitoring}

If site is a <u>non-responder</u>:

Treatment start:

Provide implementation strategy A for all sites

After 3 months:

If site is a **responder**:

Tailoring variable

Then, strategy ={low-level monitoring} If site is a <u>non-responder</u>:

Treatment start:

Provide implementation strategy A for all sites

After 3 months:

If site is a <u>responder</u>:



Then, strategy =**{low-level monitoring}**

If site is a <u>non-responder</u>:

Treatment start:

Decision rule

entation strategy A to all sites

After 3 months:

If site is a <u>responder</u>:

Then, strategy ={low-level monitoring}

If <u>non-responder</u>:

Treatment start:

Provide implementation strategy A

After 3 months:

If site is a <u>responder</u>:

Then, strategy ={low-level monitoring}

utcomes

If site is a <u>non-responder</u>:

Often insufficient evidence/theory to decide:

- Which strategy(ies) should I **start with**?
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Sample size example

N= sample size for the <u>entire</u> trial



α = .05 (two sided), power =1 – β =.80

*Assumptions: equal variances, normality, equal # in each group, no dropout.

Als in implementation research

- **Treatment** = implementation strategy(ies)
- Unit of randomization = site/provider
- Outcome = adoption/uptake (*implementation*);
 patient clinical improvement (*effectiveness*)

Als in implementation research

EXAMPLE

Phase 1:

Provide implementation strategy A for all sites

After 3 months:

If site is a *responder*:

Then, strategy ={low-level monitoring}

If site is a *non-responder*:

Then strategy={+ implementation strategy B}

ADEPT: Additional analyses

Compare 3 embedded Als:

- Provide EF; at 6 months, discontinue for responders at 6 months & continue EF for nonresponders
- Provide EF; at 6 months, discontinue for responders at 6 months & provide EF+IF for nonresponders
- Provide EF+IF; at 6 months, discontinue for responders & continue EF+IF for non-responders