May 16-18
Montreal, Canada

2024 CONFERENCE

10th Anniversary Edition

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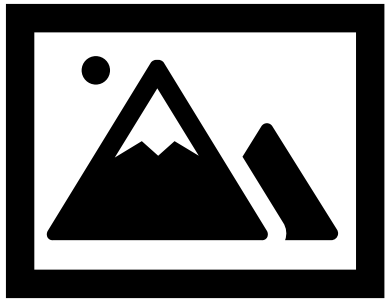
Development and Testing of Stepped Care Algorithms



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Workshop #2

Using the ORBIT Model for Research on Complex Behavioral Interventions

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Disclosures

- Research support: National Heart, Lung, and Blood Institute (USA)
- The Foundation for Barnes-Jewish Hospital (USA)
- Consulting relationships: None
- Stock equity: None
- Speaker’s bureaus: None
- Political ideology: Hopelessly confused

Using the ORBIT Model for Research on Stepped Care Algorithms

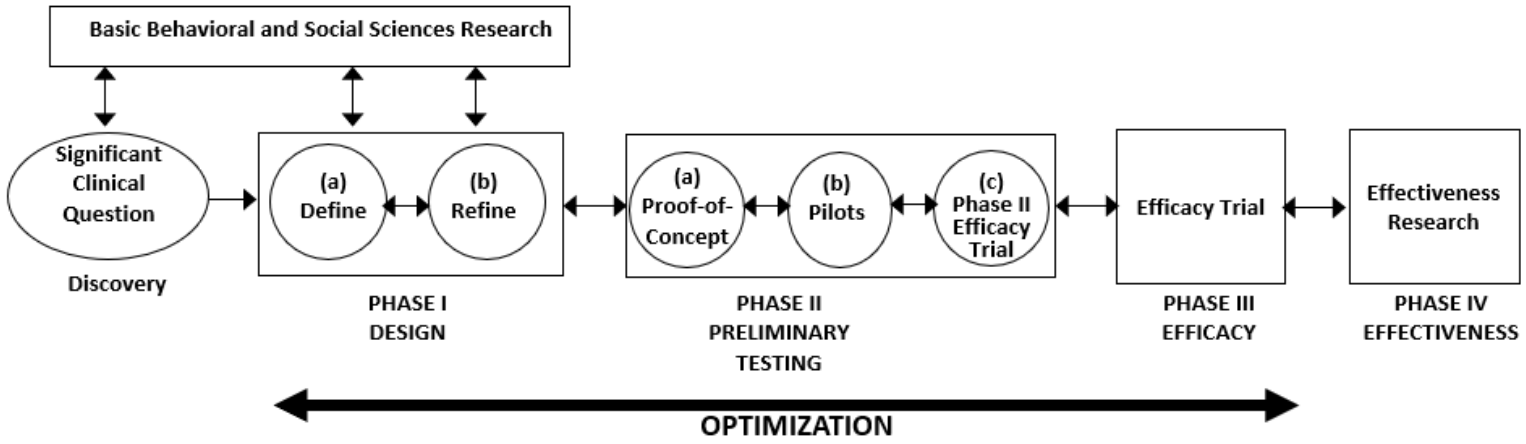


Figure 1. The ORBIT Model for Behavioral Treatment Development

- ORBIT and other translational research models are typically used to develop & test interventions.
- There aren't any models that were specifically designed for research on stepped care algorithms.
- But the ORBIT model happens to be a pretty good fit.

Behavioral Interventions for Difficult Problems Like Depression

Traditional Approach

- Develop a heavy duty, one-size-fits-all intervention (e.g., a 6-month-long weekly CBT protocol).
- Test it in a randomized controlled trial (RCT).
  - Compare it to something else – maybe supportive therapy? Who cares?
- See what happens.
- If $p<.05$, tell the world that CBT is an effective treatment for depression.
- Sell books, give lucrative C.E. workshops, be an expert on TV, live happily ever after.

Behavioral Interventions for Difficult Problems Like Depression

Traditional Approach

- We mostly cared about maximizing *efficacy.*
- We didn't care too much about costs, burdens, or harms.
- We didn't pay much attention to treatment failures.

Behavioral Interventions for Difficult Problems Like Depression

Contemporary Approach

- Develop a scalable intervention (let's call it Instant Therapy [IT]) that's simple, easy, and cheap.
- Test it for 'preliminary efficacy' in a small pilot trial.
    - Compare it to an 'attention control group' that's designed to fool and fail to help patients.
- See what happens.
- If $p<.05$, tell the world that IT is ready for clinical implementation.
- Sell books, give lucrative C.E. workshops, be an expert on TV, live happily ever after.

Behavioral Interventions for Difficult Problems Like Depression

Contemporary Approach

- Too many contemporary investigators are betting all their chips on scalability.
- They're don't care enough about efficacy.

- They're no more worried about treatment failures than the traditionalists were.

Do We *Have* to Choose Between Scalability and Efficacy?

I don’t think so.

- We can have our cake and eat it too.
- How?
- By developing **stepwise** approaches to difficult behavioral and psychosocial problems.

Two Kinds of Stepwise Approaches

Adaptive Interventions

- Single complex intervention with multiple components and/or multiple dosage levels.
- Components and/or dosage levels are deployed sequentially.
- Nonresponders to initial components or doses are given other components or additional doses.

Stepped Care Algorithms

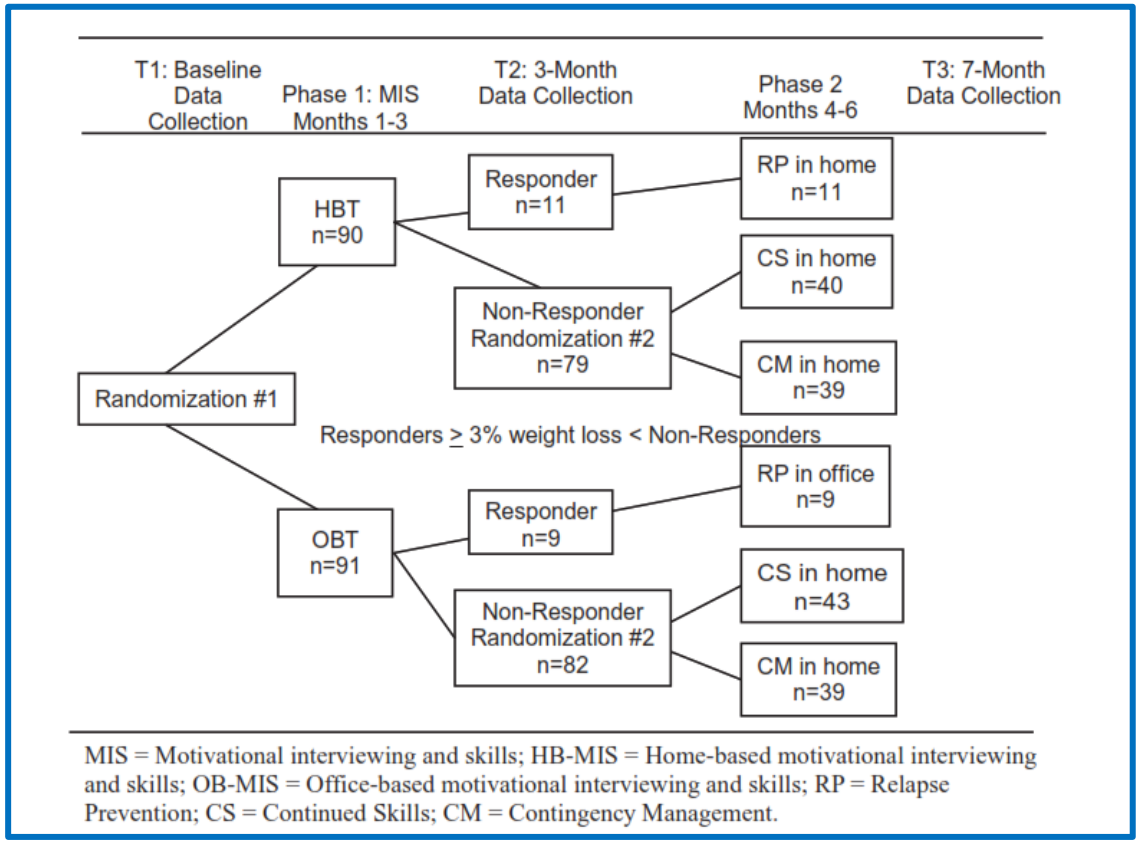
- Multiple interventions
- Interventions are deployed sequentially.
- Nonresponders to first-step intervention receive a second-step intervention.
- Nonresponders to second-step intervention receive a third step intervention.

Two Kinds of Stepwise Approaches

To save time, I'm going to focus primarily on **stepped care**.

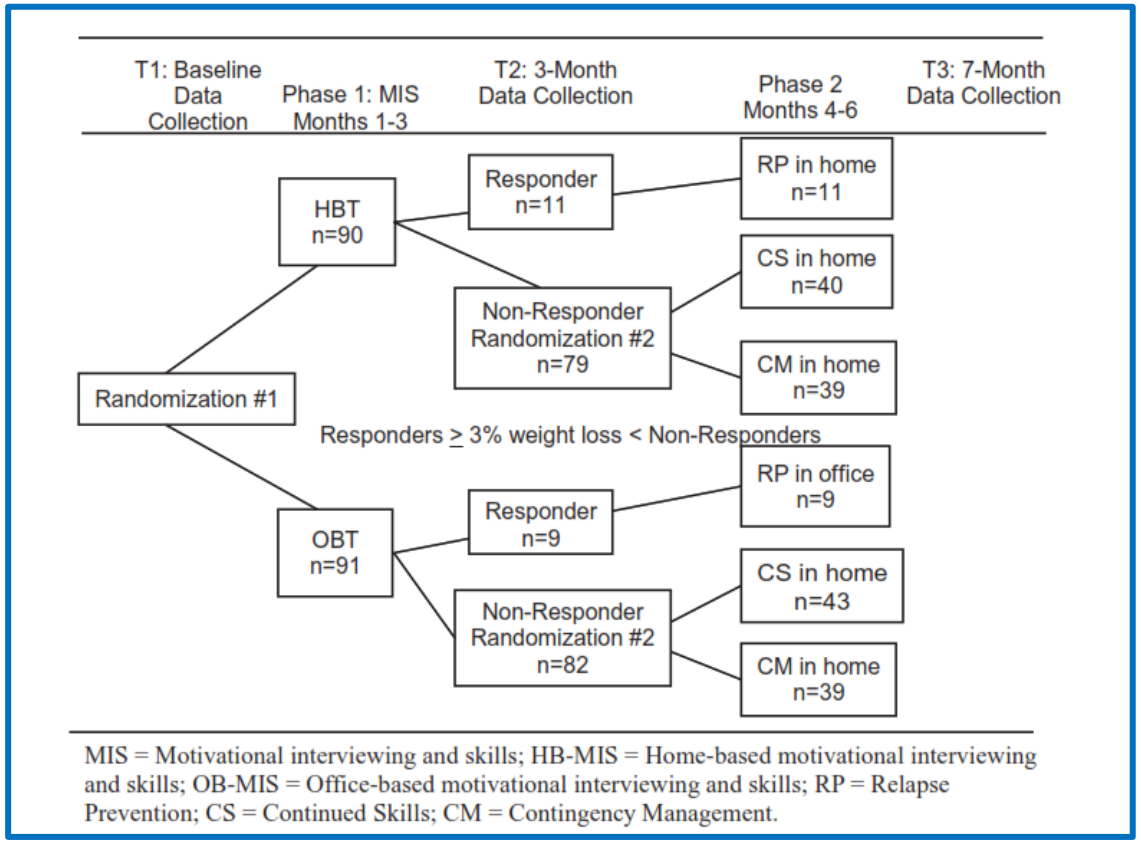
- Want to learn more about how to develop and test **adaptive interventions**?
- The **Multiphase Optimization Strategy (MOST)** includes some great tools for that.
  - E.g., **Sequential, Multiple Assignment, Randomized Trial (SMART) designs**
- See, for example:
  - Kidwell KM, Almirall D. Sequential, Multiple Assignment, Randomized Trial Designs. *JAMA* 2023;329(4):336-337. PMID: 36692577.
  - https://d3c.isr.umich.edu
  - https://cadio.org

Example of a SMART for an Adaptive Weight Loss Intervention



- Naar S., et al. Outcomes from a sequential multiple assignment randomized trial of weight loss strategies for African American adolescents with obesity. *Annals of Behavioral Medicine* 2019;53:928-938.

Example of a SMART for an Adaptive Weight Loss Intervention



Notice the low response rates at T2.

HBT: 12%

OBT: 10%

Some patients who didn't respond by T2 *did* respond by T3.

But many patients were still nonresponders at T3.

Adaptive interventions can help but they aren't a panacea for difficult problems like obesity.

- Naar S., et al. Outcomes from a sequential multiple assignment randomized trial of weight loss strategies for African American adolescents with obesity. *Annals of Behavioral Medicine* 2019;53:928-938.

Unique Blend: A Heavy Duty Yet Adaptive Intervention

ORIGINAL ARTICLE

Sequential Interventions for Major Depression and Heart Failure Self-Care: A Randomized Clinical Trial

Kenneth E. Freedland, PhD; Judith A. Skala, PhD; Robert M. Carney, PhD; Brian C. Steinmeyer, MS; Eugene H. Rubin, MD, PhD; Michael W. Rich, MD

Circulation: Heart Failure 2022;15:e009422. PMID: 35973032

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CBT for Major Depression in Outpatients with Heart Failure

Intervention

- CBT delivered in person and/or remotely by mental health professionals
  - Extensive CBT training and experience; supervised by P.I.
- PHQ-9 and GAD-7 used to track weekly progress.
  - Weekly progress milestones (% improvement on the PHQ-9).
- Intensive (weekly) phase lasted 8-16 weeks.
- Maintenance (biweekly or monthly) phase lasted through Week 32.

- Adaptative elements:
  - Taper frequency after Week 8 if milestones are met.
  - Use techniques from *CT for Challenging Problems* by J.S. Beck if milestones aren't met.
  - Refer to PCP for antidepressant Rx (or Rx modification) if referral criteria met.

Primary Outcome (BDI-2 Depression Score at Week 16)

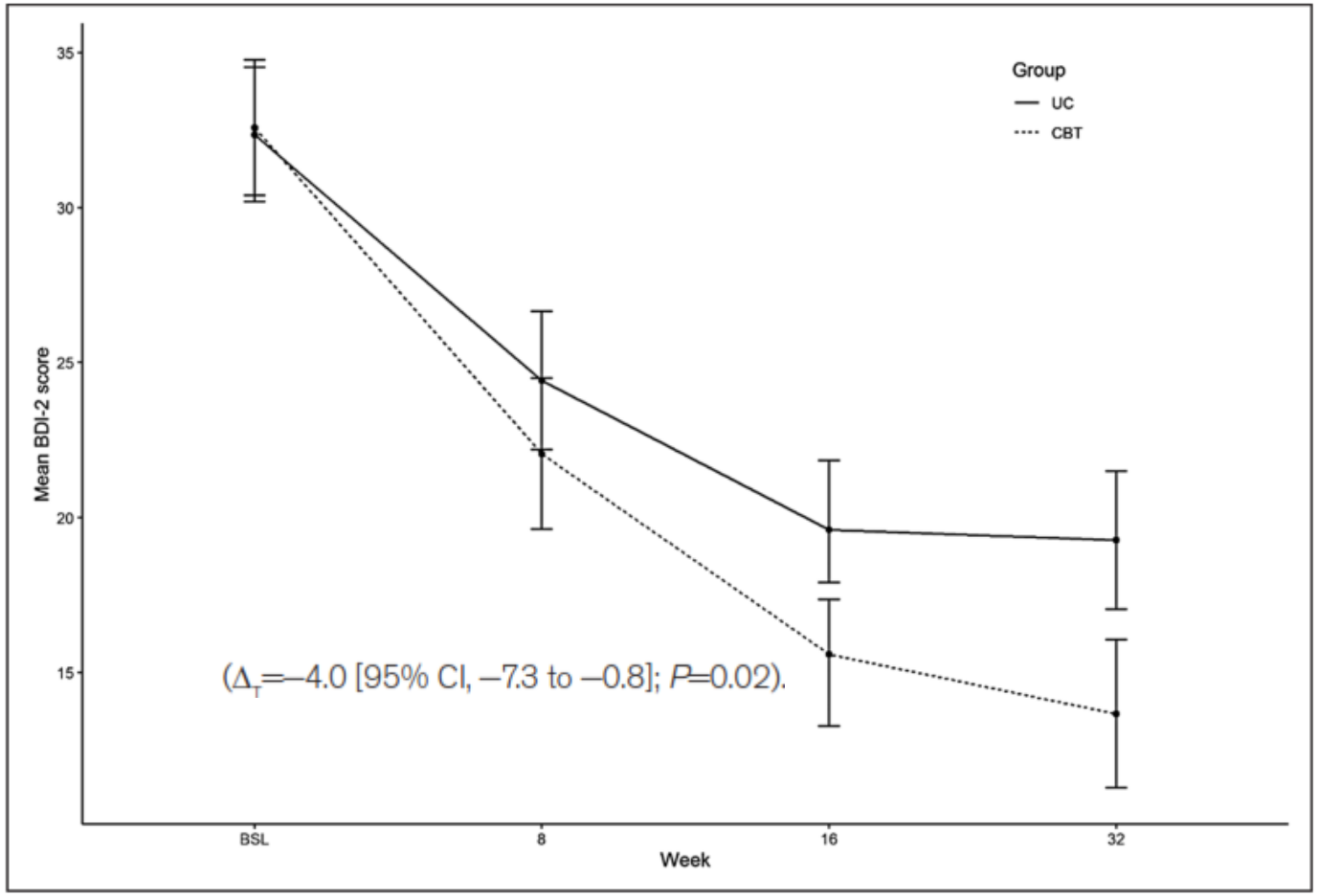

Figure 2. Scores on the Beck Depression Inventory (BDI-II) at randomization and the 8-, 16-, and 32-week follow-up visits.
CBT indicates cognitive behavior therapy; and UC, usual care.

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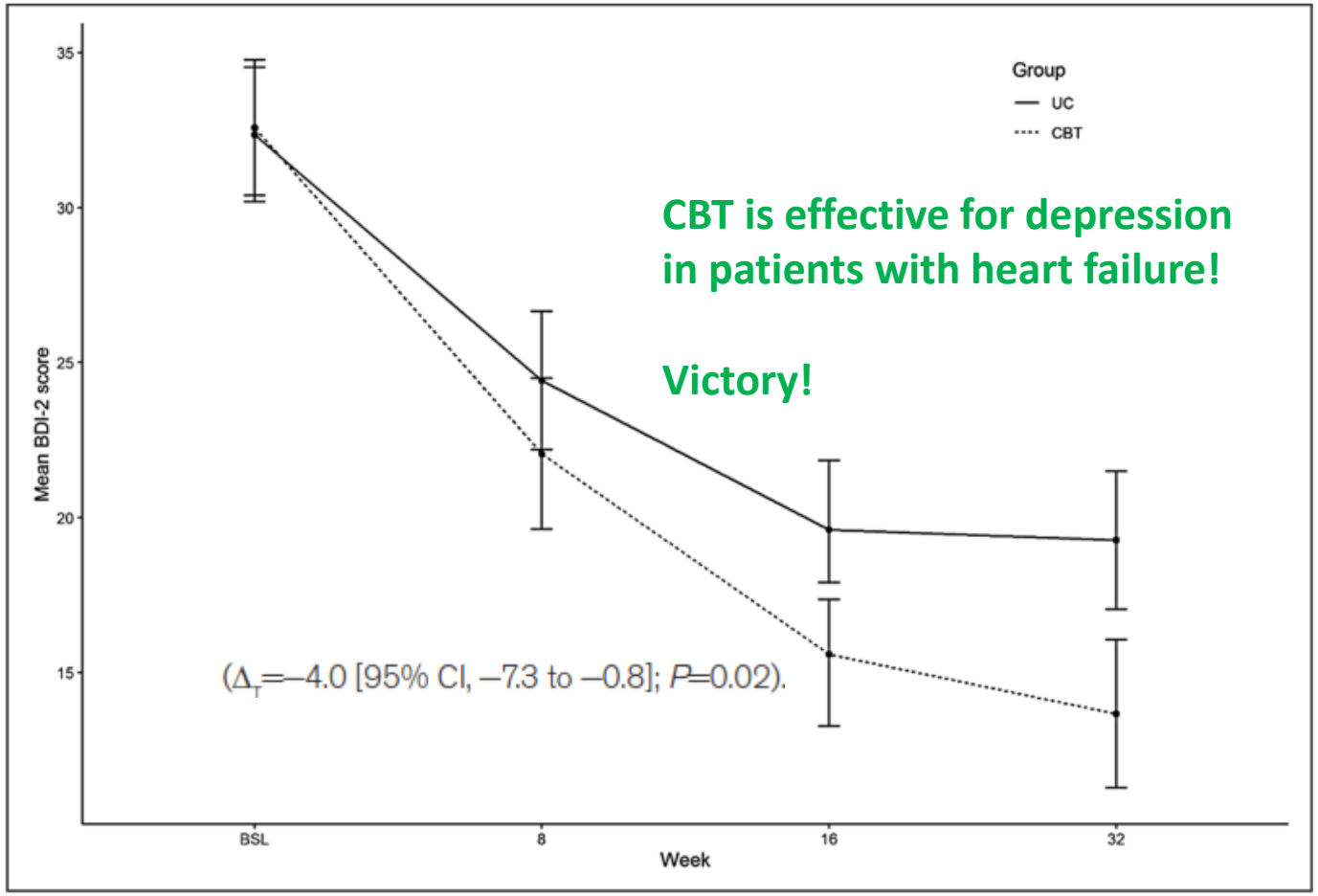

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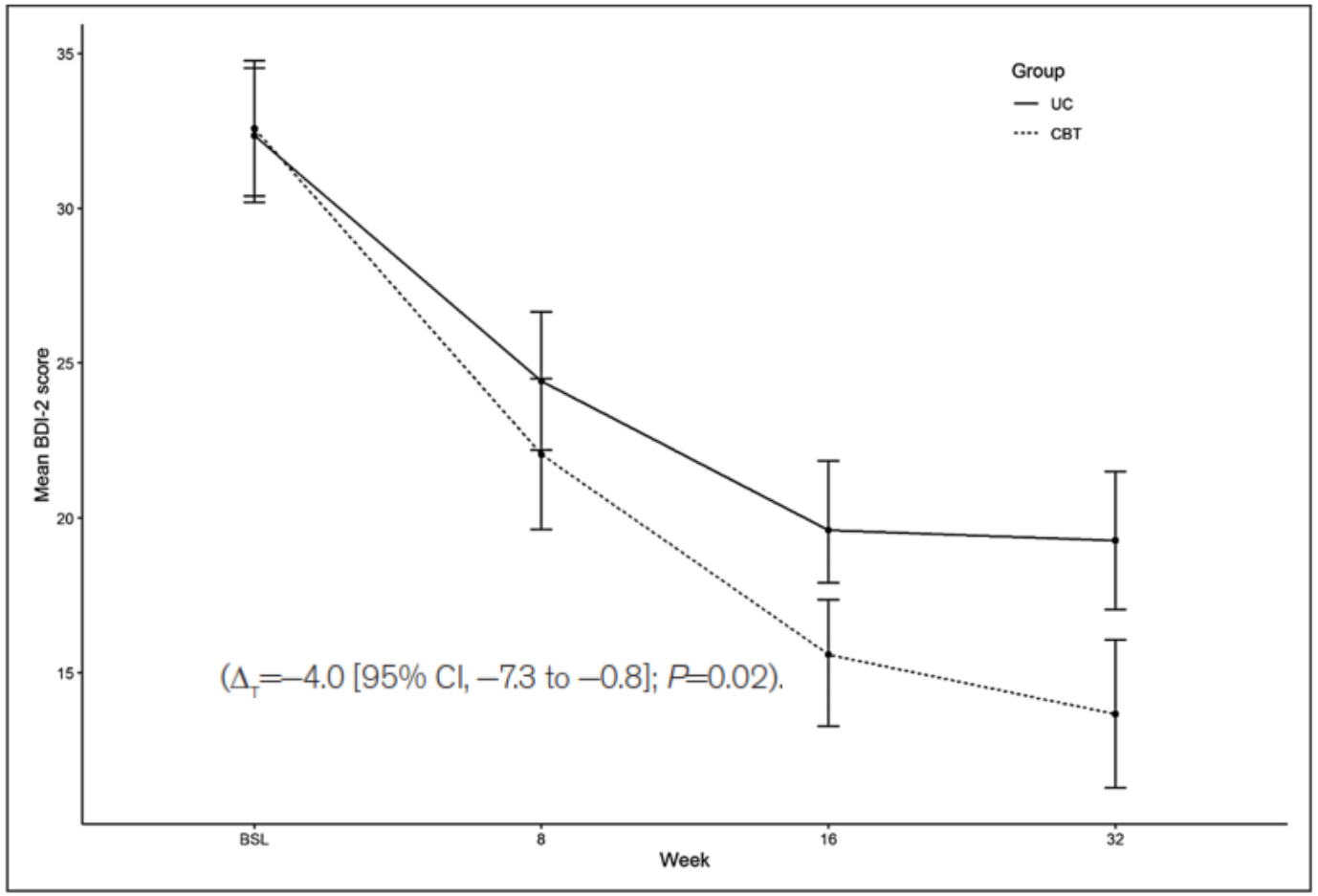

Figure 2. Scores on the Beck Depression Inventory (BDI-II) at randomization and the 8-, 16-, and 32-week follow-up visits.
CBT indicates cognitive behavior therapy; and UC, usual care.

'Successful outcome' defined as remission by Week 16.

Success rates:

UC 21%

CBT 29%

NNT 12

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CBT for Major Depression in Outpatients with Heart Failure

What's wrong with this picture?

- We used an adaptive variant of CBT; nonresponders or slow responders:
  - continued intensive Tx after others had tapered, and
  - received techniques described in *CT for Challenging Problems.*
- But it was still basically a 'heavy duty' intervention – not very scalable.

CBT for Major Depression in Outpatients with Heart Failure

What's wrong with this picture?

- And it still wasn't enough!
  - 71% of patients failed to remit
  - Even after receiving up to 32 weeks of individual CBT with a highly trained professional.
  - NNT = 12; for every 12 pts. treated with CBT, only one more remitted than if they'd gotten UC.
- Even if this approach could be widely implemented in clinical practice settings,
  - we'd be subjecting 71% of patients to an expensive, burdensome, and protracted treatment failure in order to enable 29% of patients to achieve remission.

CBT for Major Depression in Outpatients with Heart Failure

What if we had bet all of our chips on scalability and ignored efficacy?

- We might have tried a developing simpler intervention that…
  - Took nowhere near 16-32 weeks to complete – maybe 4-6 weeks?
  - Didn't require highly trained, experienced mental health professionals.
  - Was inexpensive and convenient.
- But if you agree that a 29% success rate for adaptive CBT ain't so great,
  - Imagine how much *worse* our success rate might be with this lightweight, scalable intervention.
  - What if it were only 25%? Or 21%?
- Sure it's scalable – but would it be worth implementing?

Stepped Care for Major Depression in Patients with Heart Failure

We don't yet have a stepped care algorithm for depression in heart failure.

- But if we did, what might it look like?
  - Step 1: A scalable, brief intervention that would suffice for the most responsive patients.
  - Step 2: A less scalable intervention that would suffice for many of the Step 1 nonresponders.
  - Step 3: An aggressive intervention that would work for some of the Step 2 nonresponders.
  - etc.?

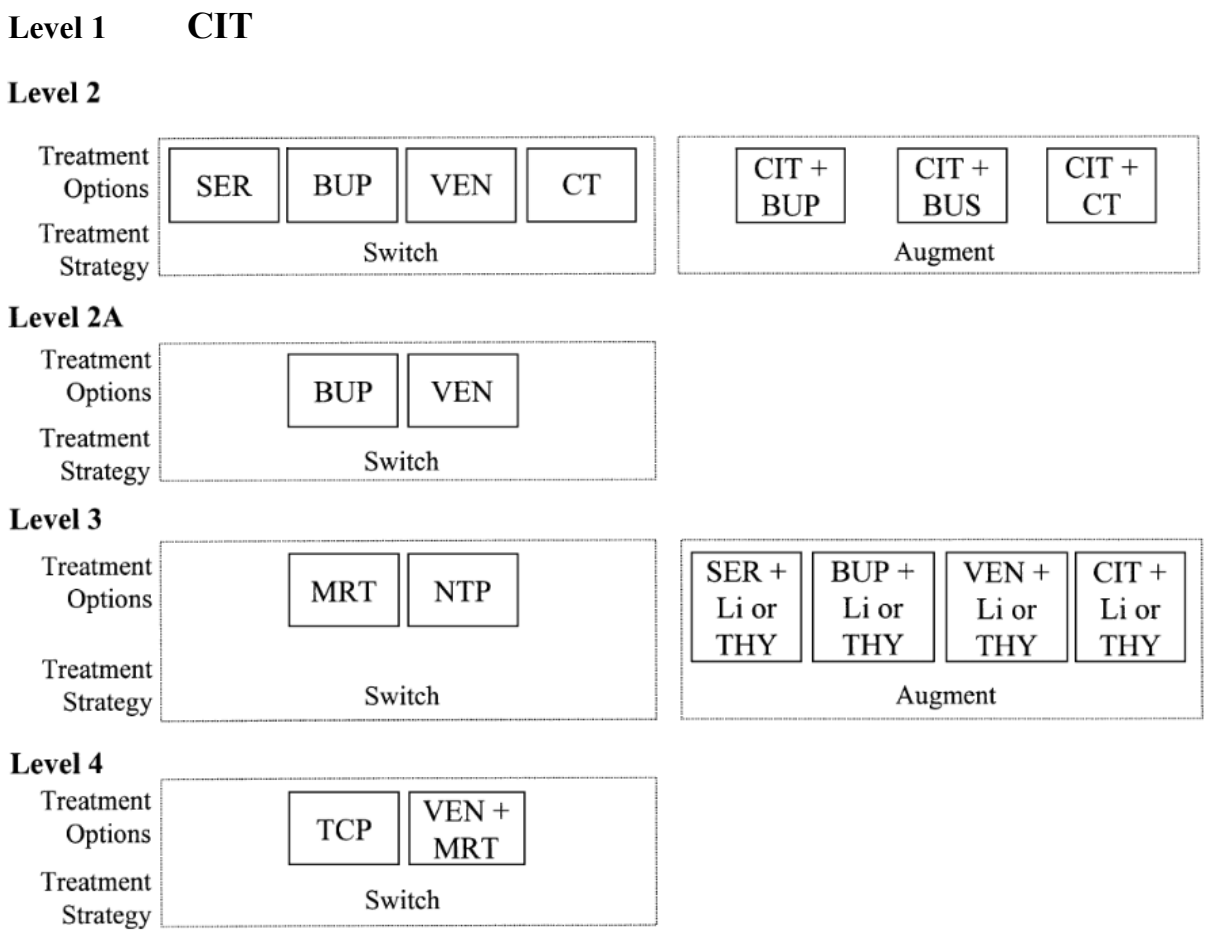
- Pros and Cons:
  - Fewer patients need Step *i*+1 than need Step *i.*
  - The success rate will probably *drop* at each step while the cost (and maybe risk) will increase.
  - But the *cumulative* success rate for the stepped care algorithm will exceed the Step 1 rate.
  - And the overall cost, burden, and risk will be lower than a one-size-fits-all, heavy duty Tx.

One of the Best-Known Examples of Stepped Care Research

Many patients have *treatment-resistant* major depression.

- 'Treatment-resistant' is defined as failing to respond despite adequate trials of ≥2 treatments.
- The landmark **Sequenced Treatment Alternatives to Relieve Depression (STAR*D)** trial tested an elaborate stepped care algorithm for patients with chronic or recurrent depression.
- Over 4,000 adult outpatients enrolled in STAR*D over a seven-year period;
  - 2,876 were treated.
  - Every enrolled patient started on citalopram, a common SSRI antidepressant.
- Almost 400 papers about STAR*D – including original empirical reports, review papers, editorials, etc. have been published since 2003.

STAR*D Stepped Care Algorithm (Rush et al., 2004)



BUP	Bupropion
BUS	Buspiron
CIT	Citalopram
CT	Cognitive Therapy
Li	Lithium
MRT	Mirtazapine
NTP	Nortriptyline
TCP	Tranylcypromine
THY	Thyroid Hormone
VEN	Venlafaxine

STAR*D: Level 1 (Citalopram) Outcomes

n=2,876 outpatients with chronic or recurrent major depression

- **Results**
- **28% remission rate (HAM-D)**
- 33% remission rate (QIDS-SR)
- 47% response rate (QIDS-SR)

- The dose was carefully escalated, up to the optimal 60 mg/day if possible.

- The results are similar to those of many short-term efficacy trials of SSRI antidepressants.

- 72% of patients did not remit, despite receiving a widely-prescribed SSRI antidepressant.

STAR*D: Cumulative Outcomes

The cumulative (overall) outcomes are controversial, still being debated.

- The STAR*D Investigators originally reported a **67% cumulative remission rate**.
- The most pessimistic analysis: **35% cumulative remission rate** (Pigott et al., *BMJ Open* 2023).
- The most optimistic analysis (Sakurai et al., *World Psychiatry* 2024):
  - **54% cumulative remission rate at 90 days**
  - **75% at 180 days**
  - **88% at 360 days**
- **Even the most pessimistic cumulative outcomes are better than citalopram monotherapy.**

Some Lessons for Us from STAR*D

- Stepped care algorithms can stitch together some very different ingredients (e.g., drugs and CBT).
  - So can adaptive interventions (e.g., automated text messages and peer counseling).
- Stepwise approaches
  - Can help patients whom monotherapies fail to help.
    - Including our best, heavy-duty, one-size-fits-all monotherapies.
  - But they don't necessarily help everybody.
    - Remember the ones who get left behind even by complex stepwise approaches.
    - Further research is needed to help them.
    - E.g., advanced therapies for depression such as TMS, VNS, and neurosteroids.
- Stepwise approaches can help to resolve tensions between scalability and effectiveness.

How Can ORBIT Help?

If you're working on a hard problem like obesity, depression, or physical inactivity:

- Start thinking about stepwise approaches, if you haven't already been doing so.
- Even if a stepwise approach already exists, there's probably plenty of room for improvement.
- What if one doesn't yet exist?
  - Maybe only monotherapies have been tried so far.
  - Maybe some combinations therapies have been tried, but not in stepwise fashion.

How Can ORBIT Help?

If you're working on a hard problem like obesity, depression, or physical inactivity:

- Where should you start?
  - Start with the first step (i.e., a first-step intervention).
  - Focus on scalability – low cost, low burden, but still therapeutic.
  - Be wary of watering down your primary outcome.
    - Aim for *clinically meaningful* success at the level of individual patients.
  - But aim also for a *realistic* first-step success rate (e.g., 20-30%) in treated groups.
    - And learn from the majority of patients who will *not* succeed.
    - Try to understand what *they* might need and respond to at Step 2.
    - Try to find / develop a Step 2 intervention for them. Etc.

How Can ORBIT Help?

The ORBIT Model is directly applicable to work on Step 1 interventions.

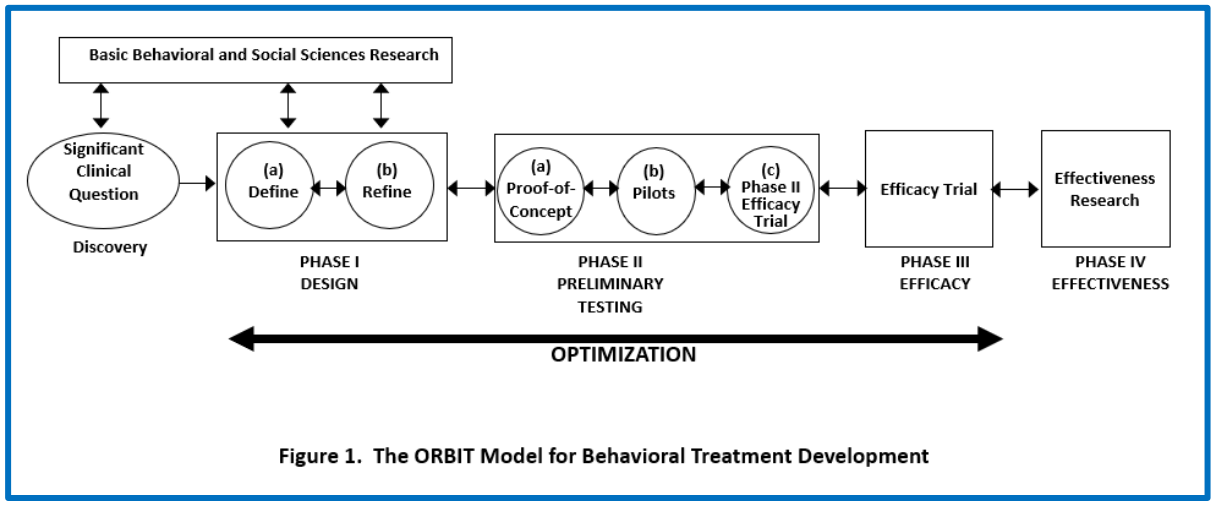


Figure 1. The ORBIT Model for Behavioral Treatment Development

How Can ORBIT Help?

- The only patients who are candidates for Step 2 are Step 1 nonresponders.

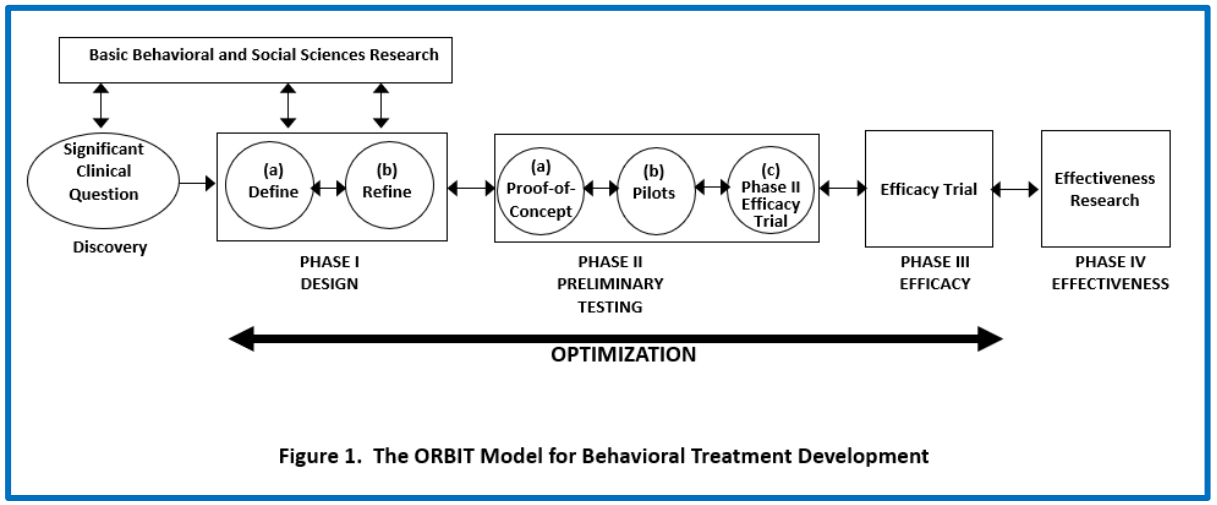


Figure 1. The ORBIT Model for Behavioral Treatment Development

- It's difficult to move beyond the Discovery and Design phases for Step 2 until you've taken the Step 1 intervention all the way through Phase IIc.

How Can ORBIT Help?

- After you've developed a scalable & modestly efficacious Step 1 intervention:

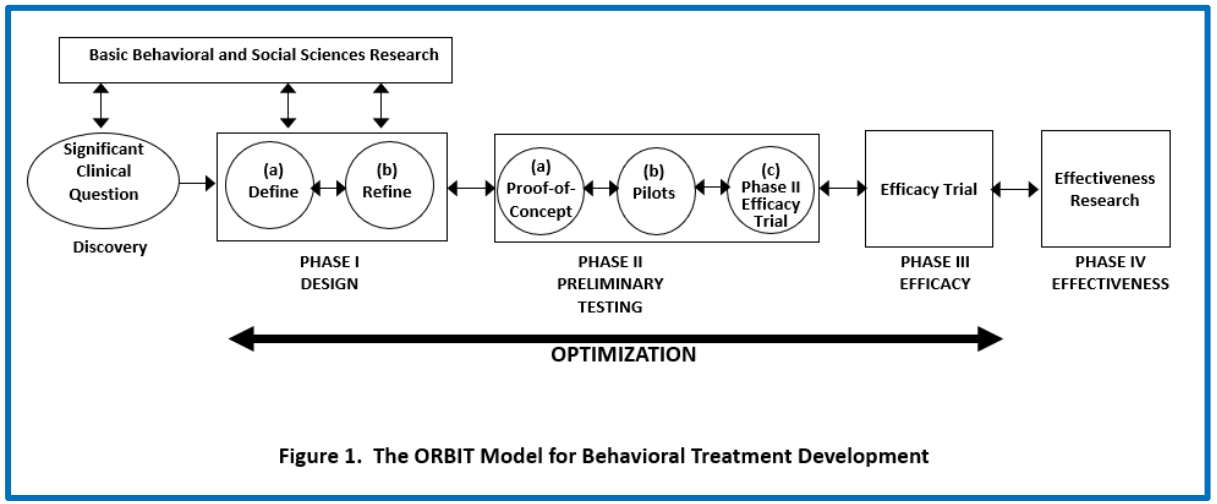


Figure 1. The ORBIT Model for Behavioral Treatment Development

- Use it to identify candidates for a Step 2 intervention.
- Take *those* patients through ORBIT as you design, refine, and test Step 2 Tx.

How Can ORBIT Help?

- If you ever reach the point where you have an effective *Step 3* intervention:

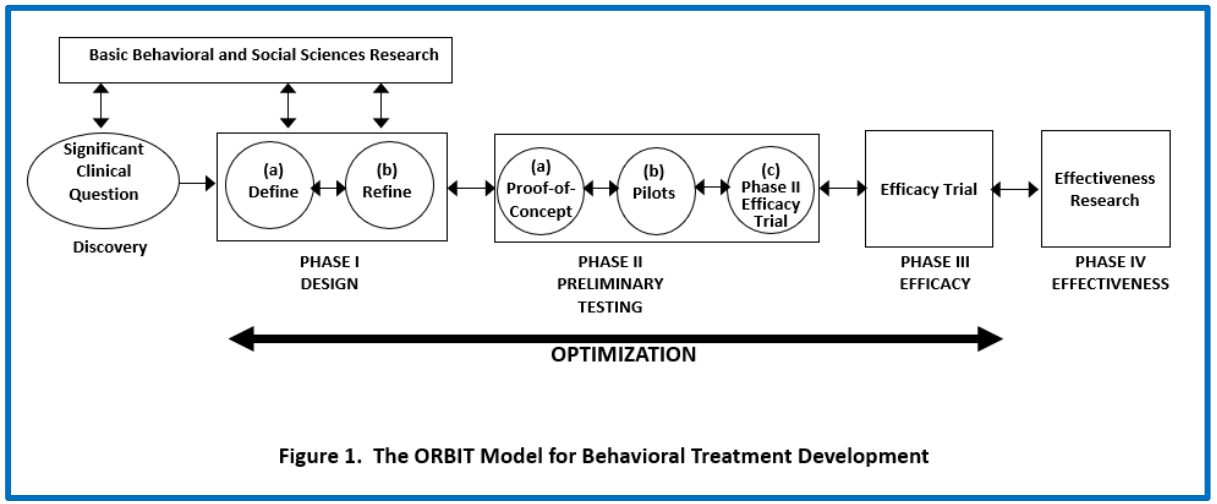


Figure 1. The ORBIT Model for Behavioral Treatment Development

- You should then test the stepped care algorithm as a whole.
- This will require a large, multicenter trial.

How Can ORBIT Help?

- If you ever reach the point where you've tested an entire stepped care algorithm,

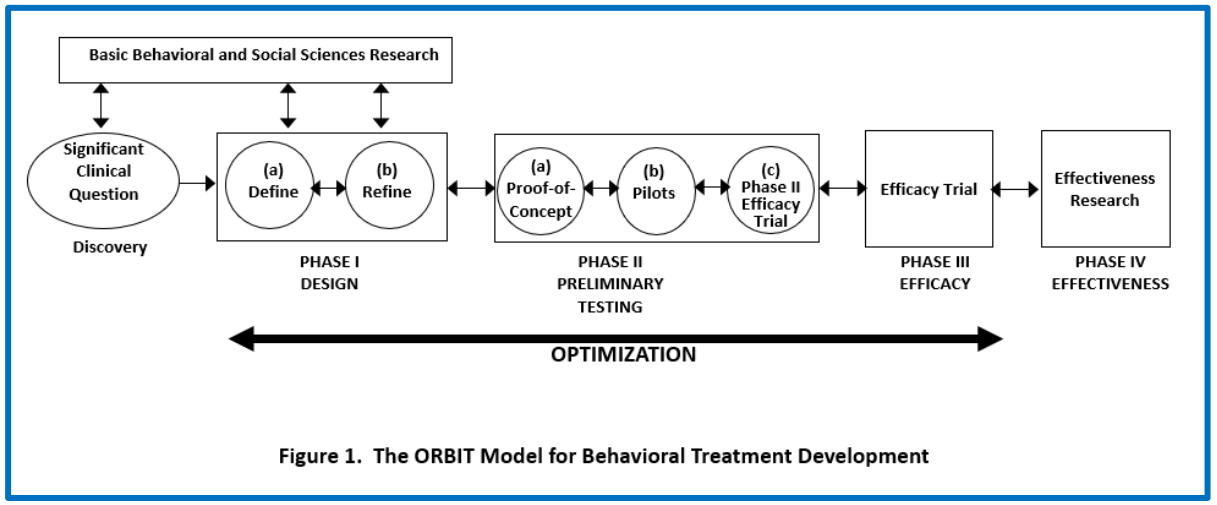


Figure 1. The ORBIT Model for Behavioral Treatment Development

- It will be time to start thinking about retirement.

Thank you !

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