Re-Engineering Precision Behavioral Therapeutics through N-of-1 Trials

International Behavioral Trials Network
May 24, 2018, Montreal, Canada
Karina Davidson, PhD & Ian Kronish, MD, MPH

Columbia University Medical Center

Agenda

9:00 AM Welcome and introductions

9:15 AM How to decide if an N-of-1 trial design is right for you?

10:00 AM Breakout Session #1:
Discuss use cases for behavioral N-of-1 trials

10:30AM Coffee break 

10:45 AM How to design an N-of-1 trial protocol

11:30 AM The Science of Behavior Change (SOBC) Initiative

11:50 AM Wrap up discussion

Acknowledgements

Funded by NCI Contract No. HHSN261200800001E

Disclosures

Ian Kronish

Funded by NHLBI, NCI, PCORI & the Irving Institute

No commercial conflicts of interest

Karina Davidson

Funded by NLM, NHLBI, NCI, PCORI & the Irving Institute

No commercial conflicts of interest

Introductions

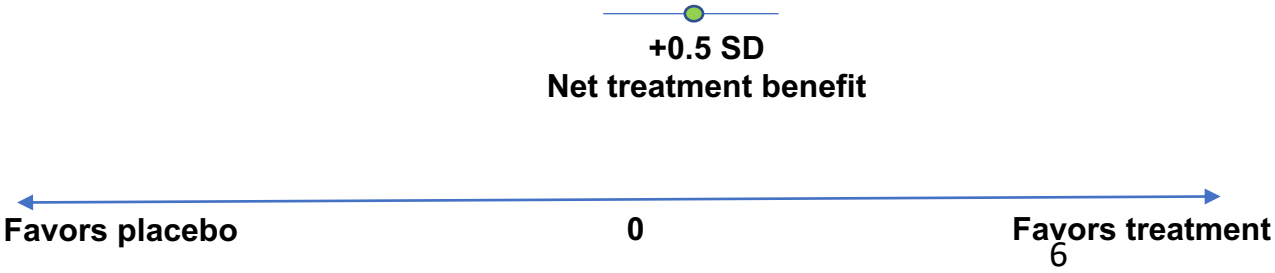
Tell us who you are?

Where are you from?
(country, university, current institution)

How is N-of-1 relevant to your current or future work?

Also,
If you already have experience / expertise in N-of-1 design, we would love to hear about your work and draw on your examples during this meeting

Conventional randomized trial



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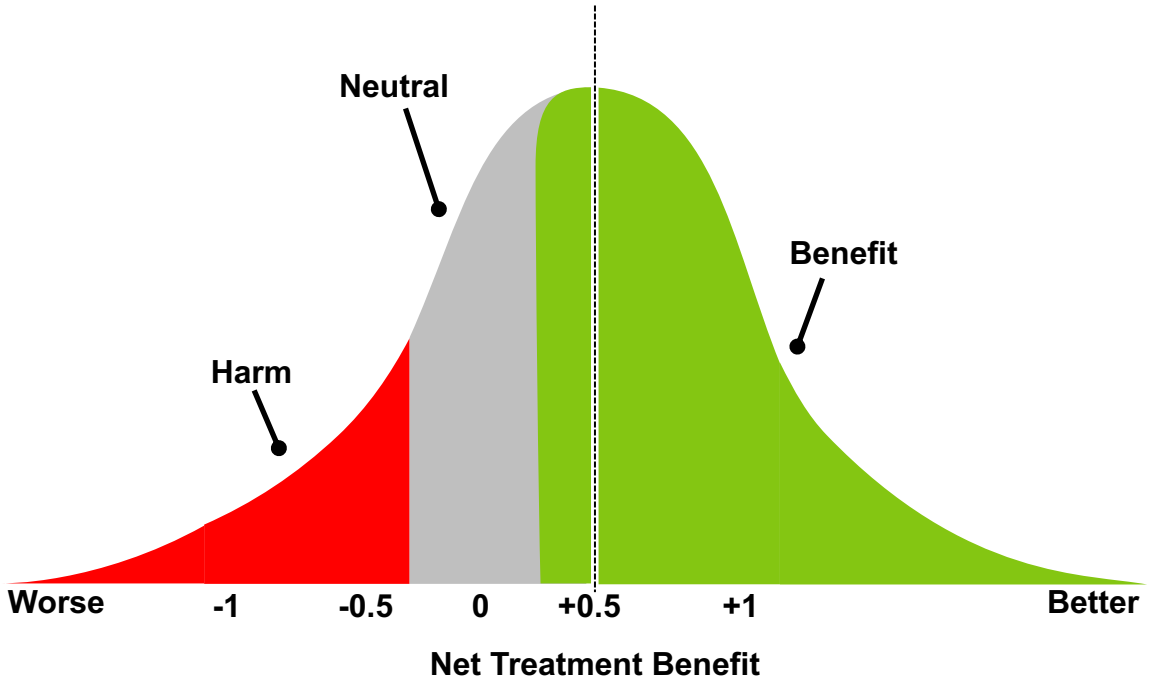
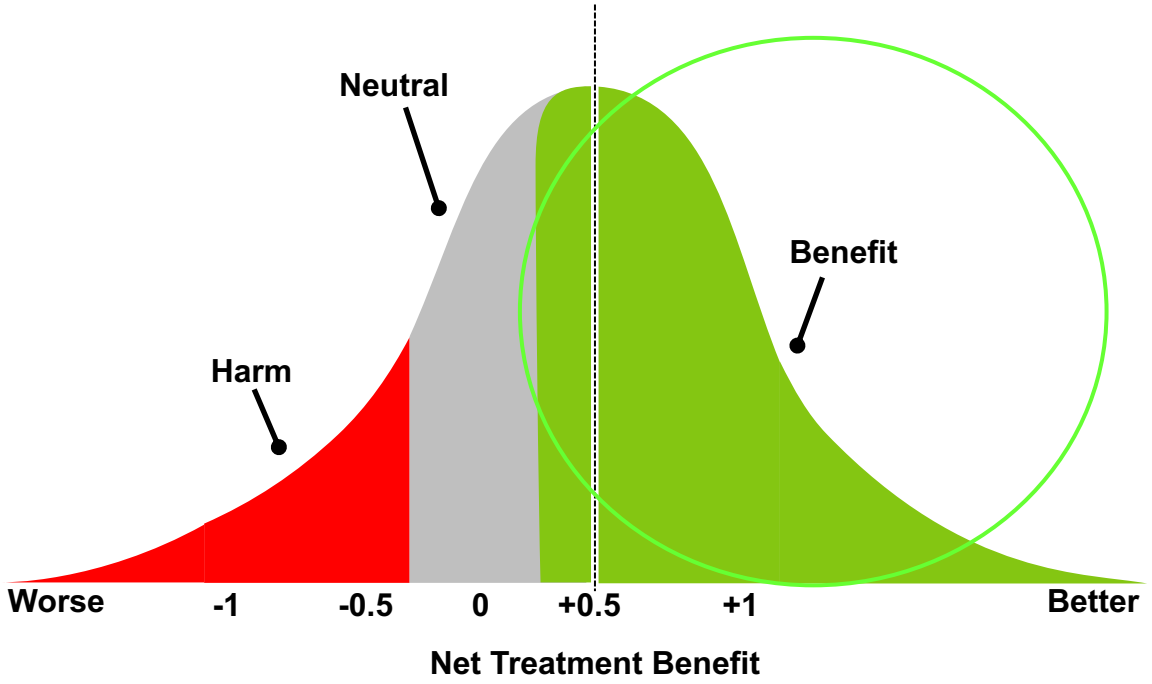
Heterogeneity of treatment effect

Positive Randomized Controlled Trial



Conventional Personalized Medicine

Use genetic or other information to identify subgroups of patients that are especially responsive to a treatment

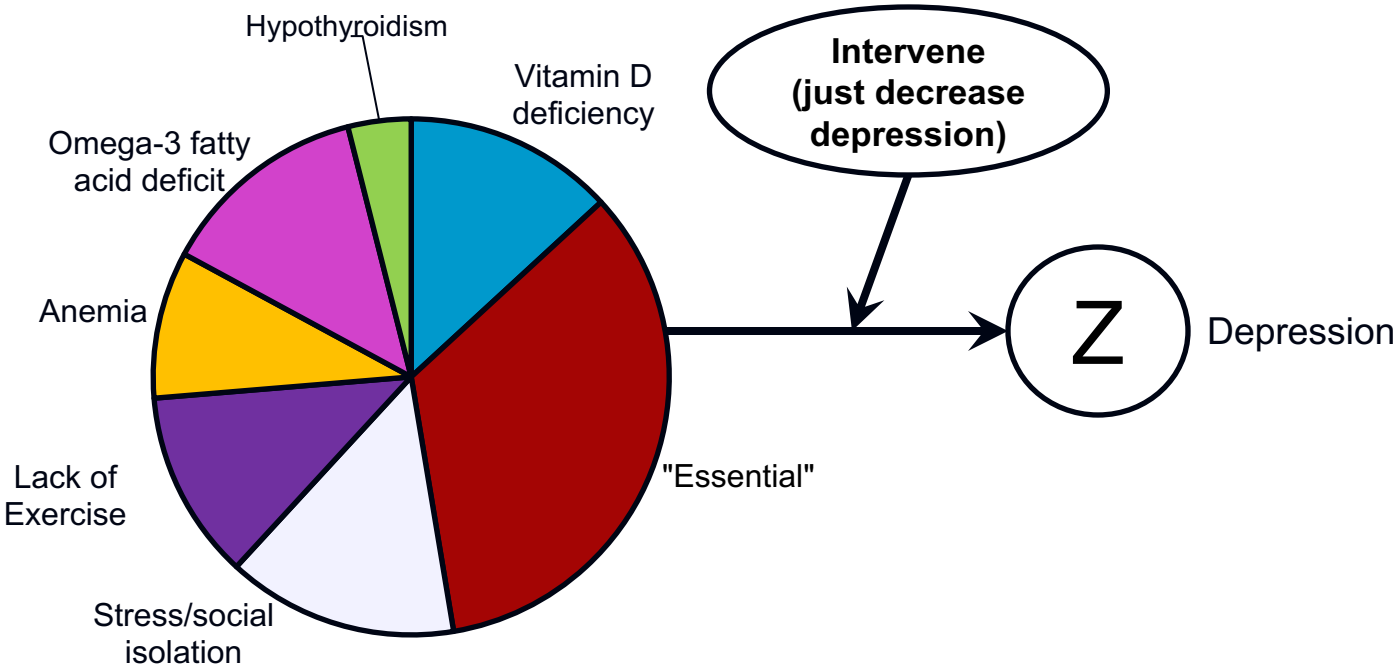


Limits of conventional personalized medicine

Genetic or other biomarkers not reliably available

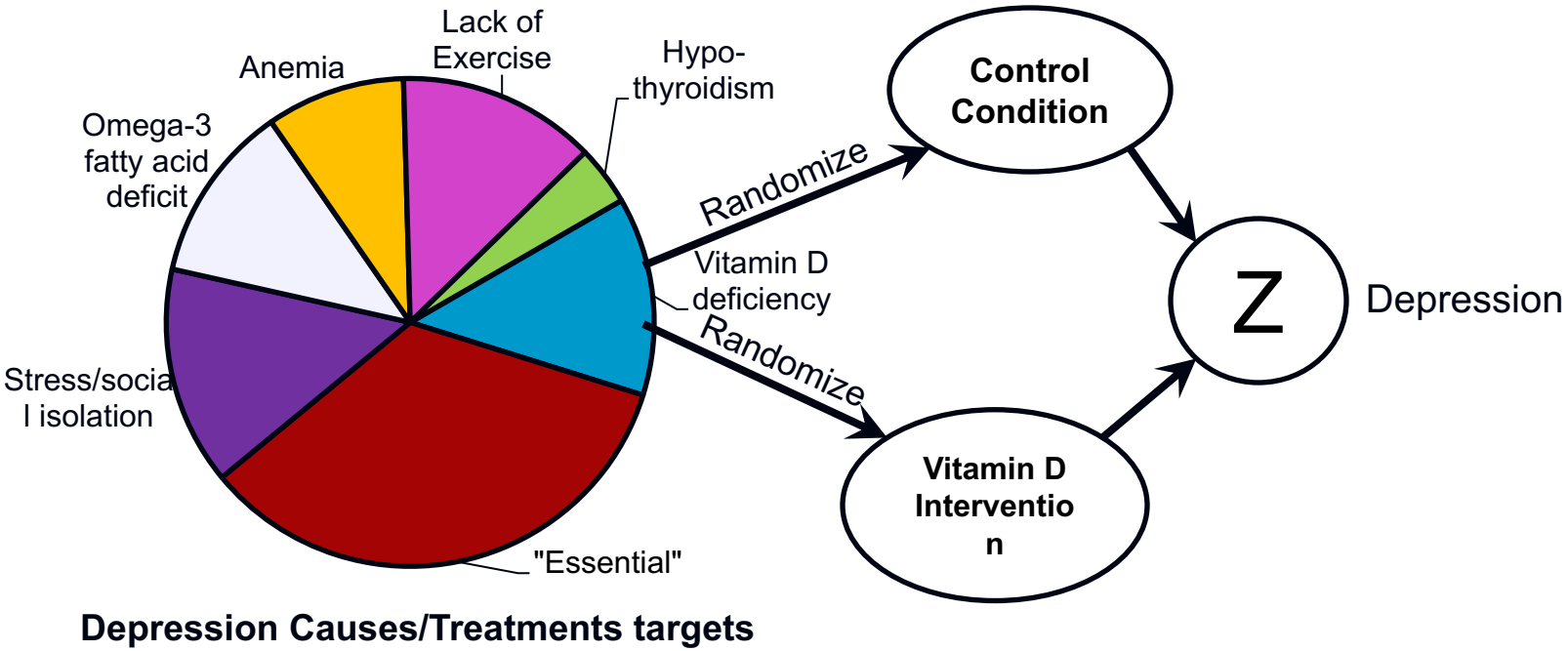
Subgrouping, not truly individualizing treatments

RCT Design 1 for Depression



Depression Causes/Treatment targets

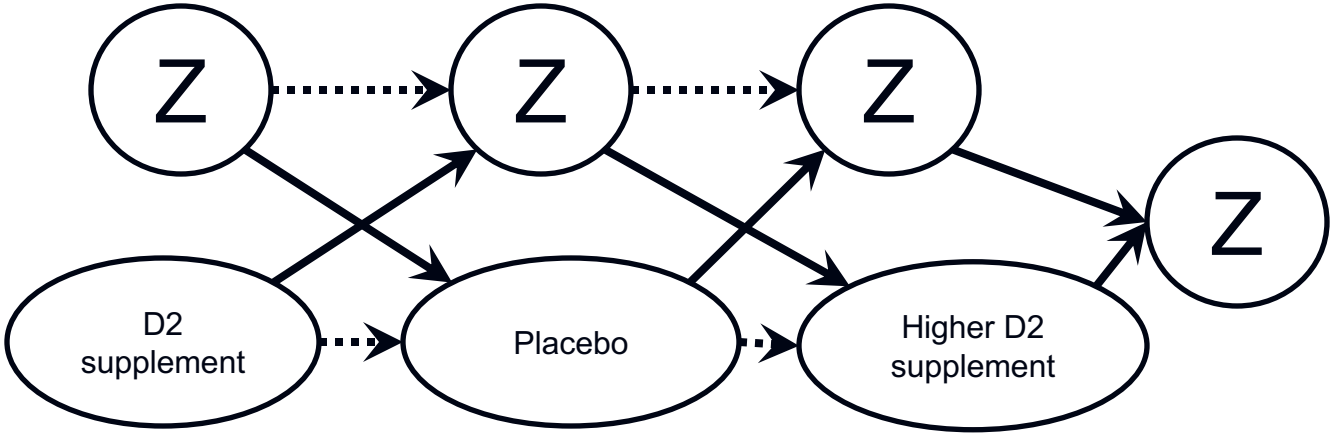
RCT Design 2 for Depression



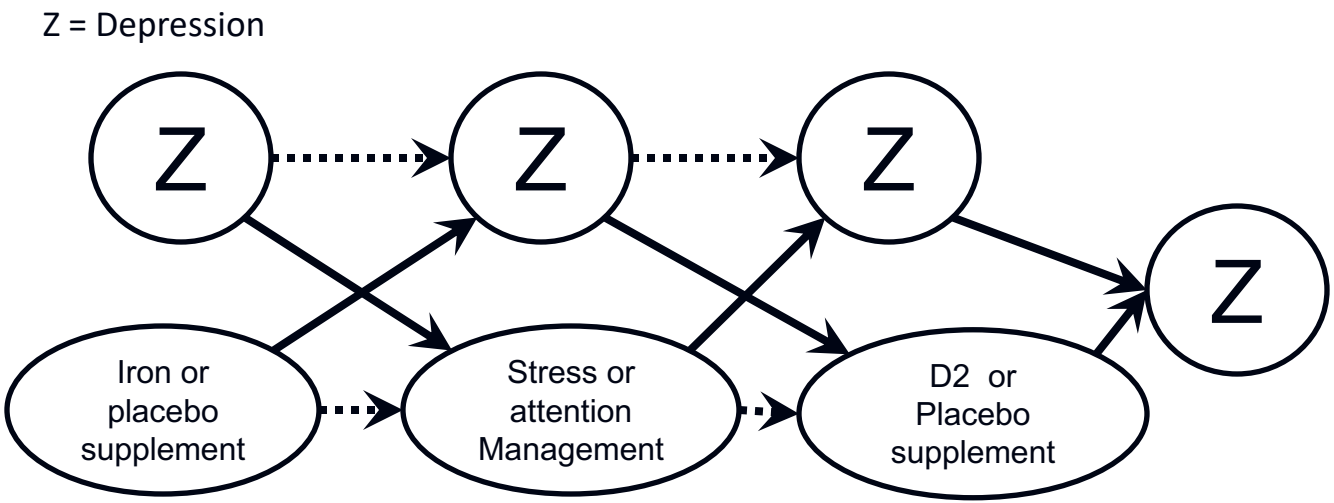
Depression Causes/Treatments targets

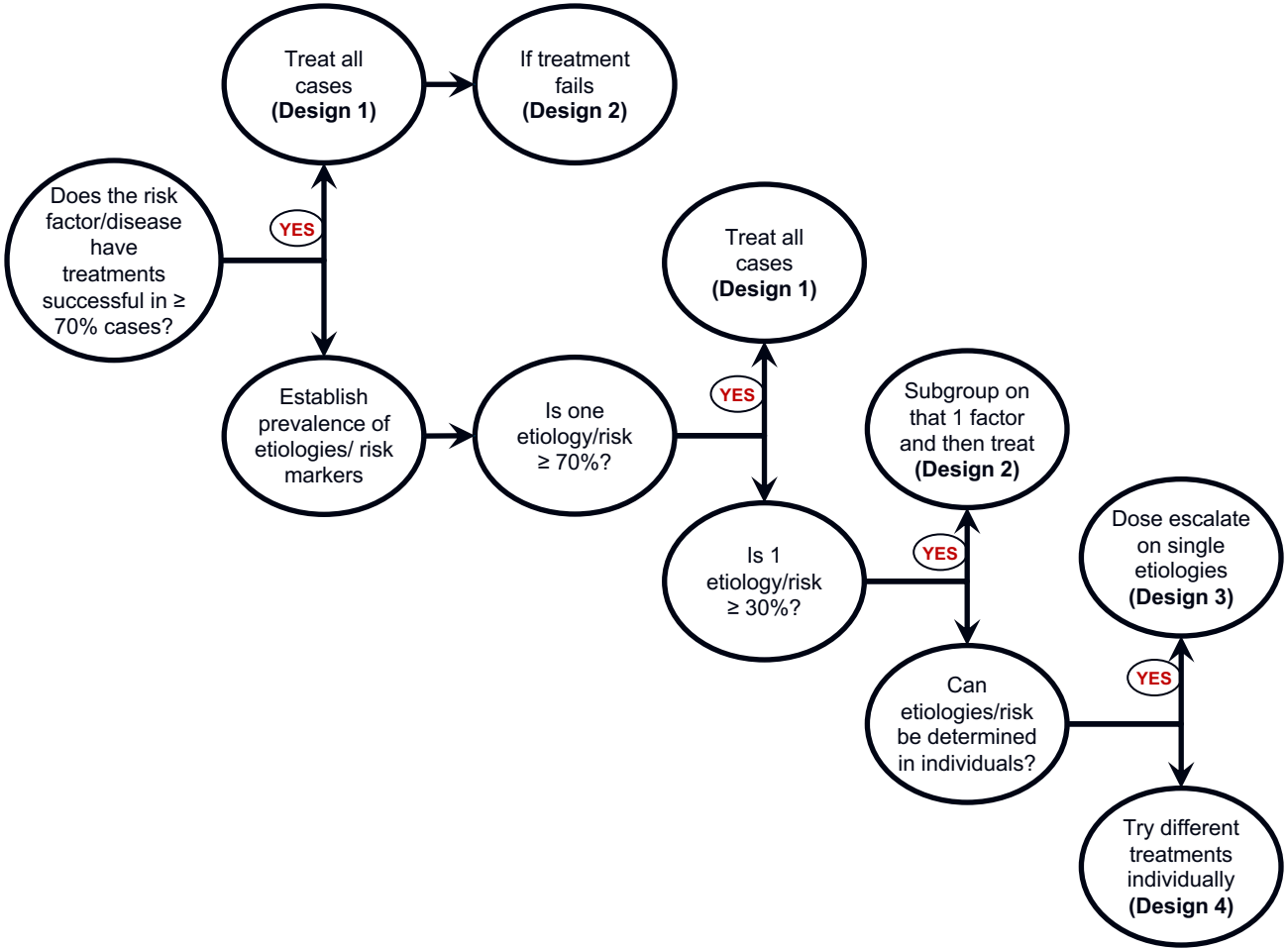
RCT Design 3 (controlled)

Z = Difficult Behavior



RCT Design 4 (controlled)




Treat all cases (Design 1)
If treatment fails (Design 2)
Does the risk factor/disease have treatments successful in ≥ 70% cases?
YES
Establish prevalence of etiologies/ risk markers
Is one etiology/risk ≥ 70%?
YES
Treat all cases (Design 1)
Is 1 etiology/risk ≥ 30%?
YES
Subgroup on that 1 factor and then treat (Design 2)
Can etiologies/risk be determined in individuals?
YES
Dose escalate on single etiologies (Design 3)
Try different treatments individually (Design 4)

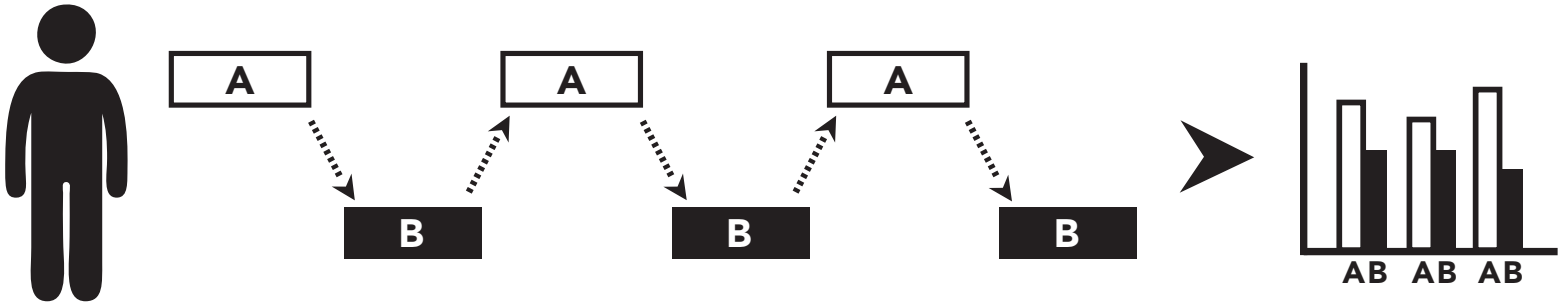
N-of-1 trials

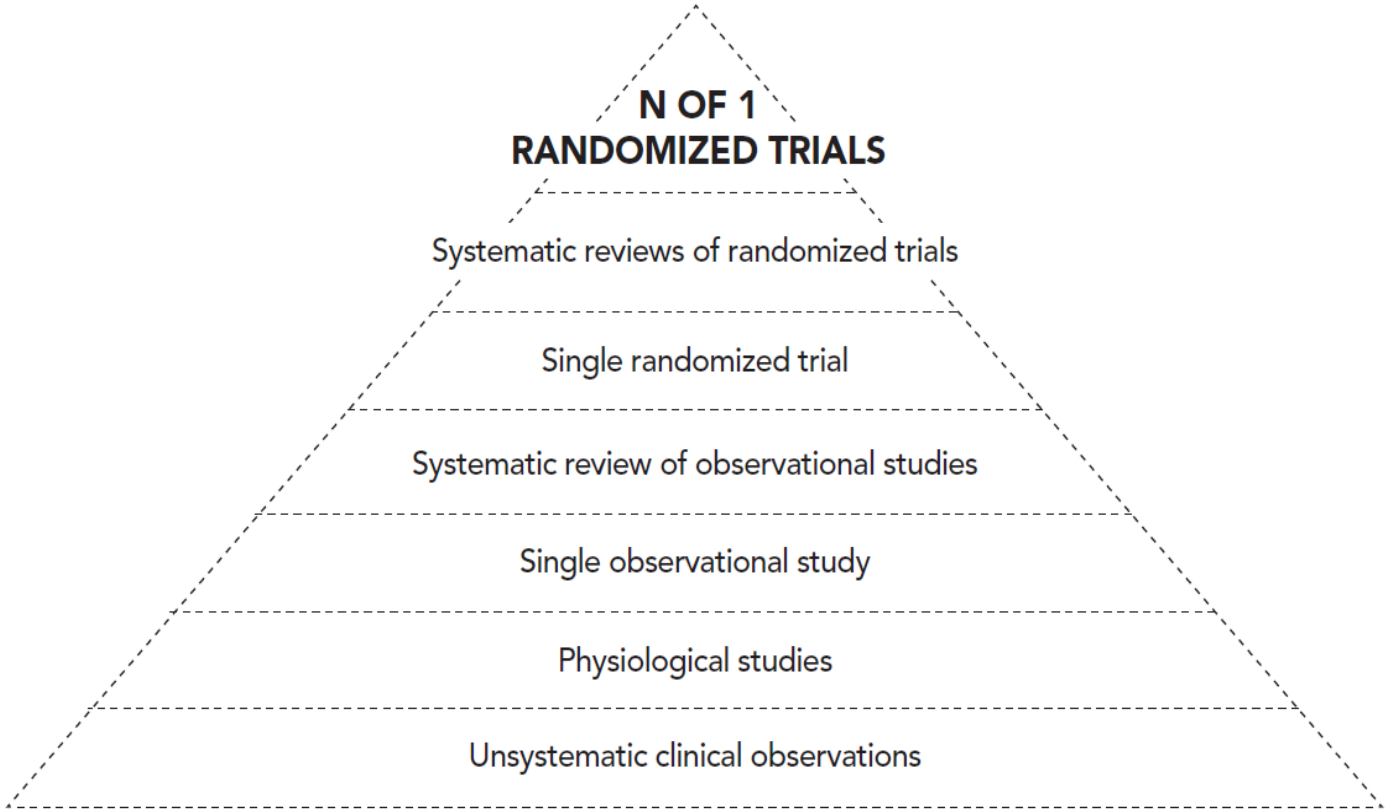
Single patient, multiple crossover trials

Systematic collection of data on treatment effects

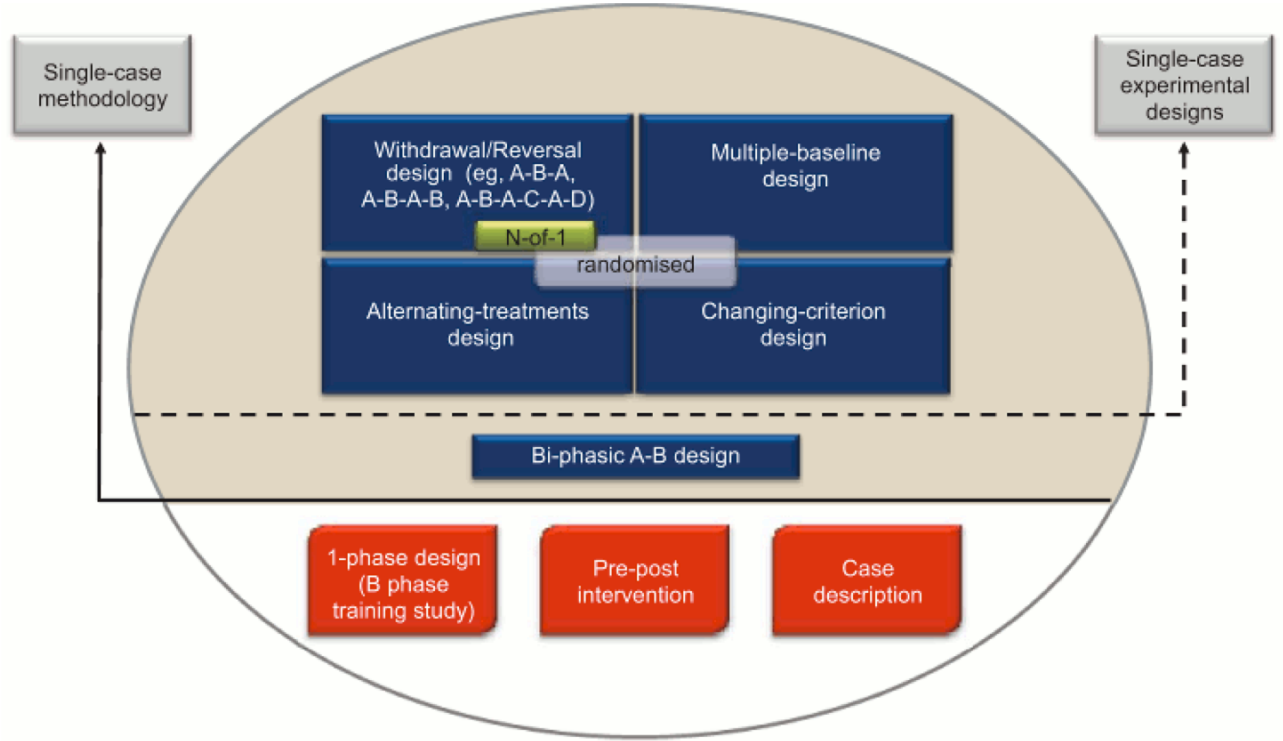
May include randomization, blinding, and placebo

Rigorous statistical analysis




N OF 1
RANDOMIZED TRIALS
Systematic reviews of randomized trials
Single randomized trial
Systematic review of observational studies
Single observational study
Physiological studies
Unsystematic clinical observations

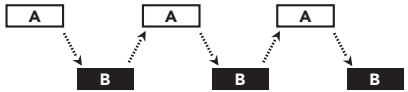
Single case designs



Tate et al. *Arch Scientific Psychol*. 2016

Personalized Trials

N-of-1 trial designed to inform patient decision-making



Systematic collection of data on treatment effects

Data visualization

Shared decision-making

Benefits of Personalized Trials

Provide patients with real-time meaningful results

Awaken patients' "inner scientist"

Results can be pooled to estimate population-level effects while relying on fewer subjects than conventional RCTs[1]

Can be incorporated into a learning health system

[1]Zucker et al. J Clin Epidemiol 1997

Aggregating N-of-1 data

Can efficiently obtain generalizable knowledge in study populations

Methods

- Meta-analysis
- Bayesian

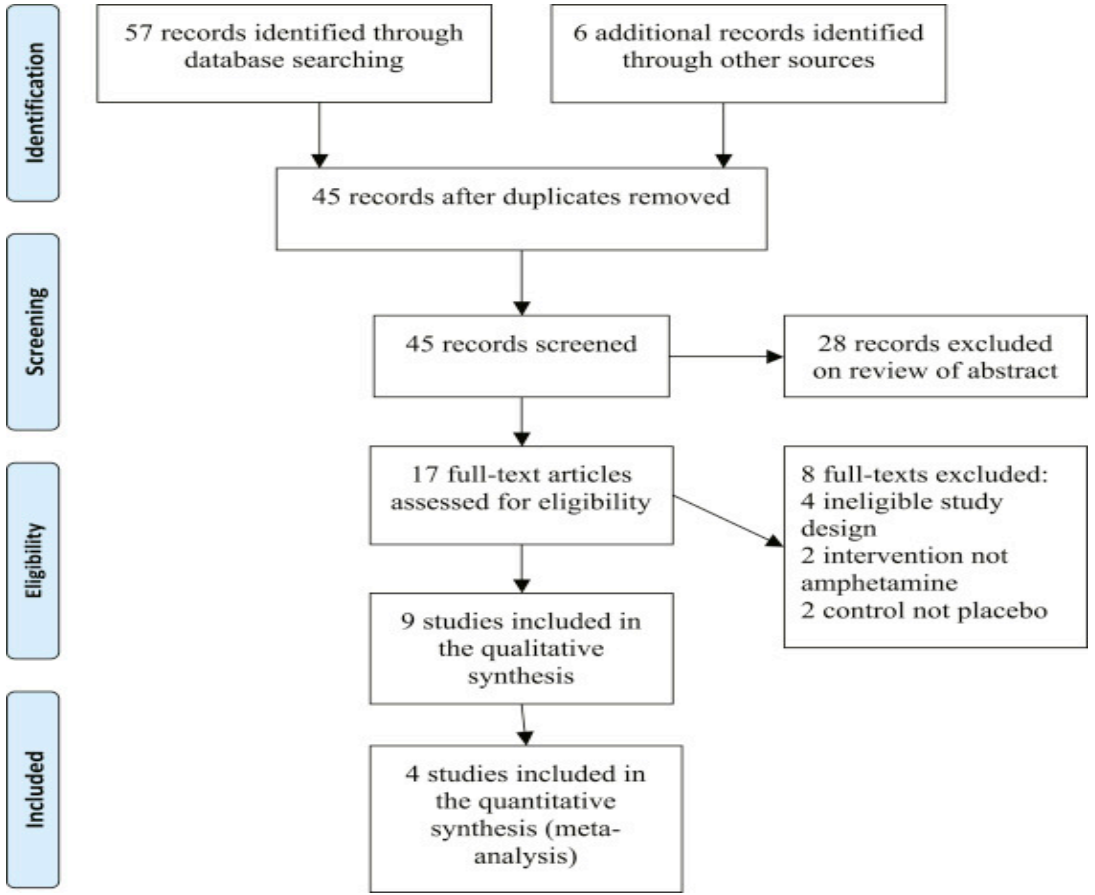
Zucker et al. *J Clin Epidemiol*, 2010;12:1312-1323.

Meta-analysis of N-of-1 Trials

1. Systematic search for N-of-1 trials with individual patient data (hopefully, registries will exist in the future)
2. Evaluate risk of bias (i.e., adequate sequence generation, allocation concealment, blinding of participants and outcome assessors, completeness of outcome data, free of biased reporting)
3. Aggregate studies
   ① Assume all blocks are exchangeable, aggregate to calculate individual treatment effect
   ② Use random effects model

Meta-analysis

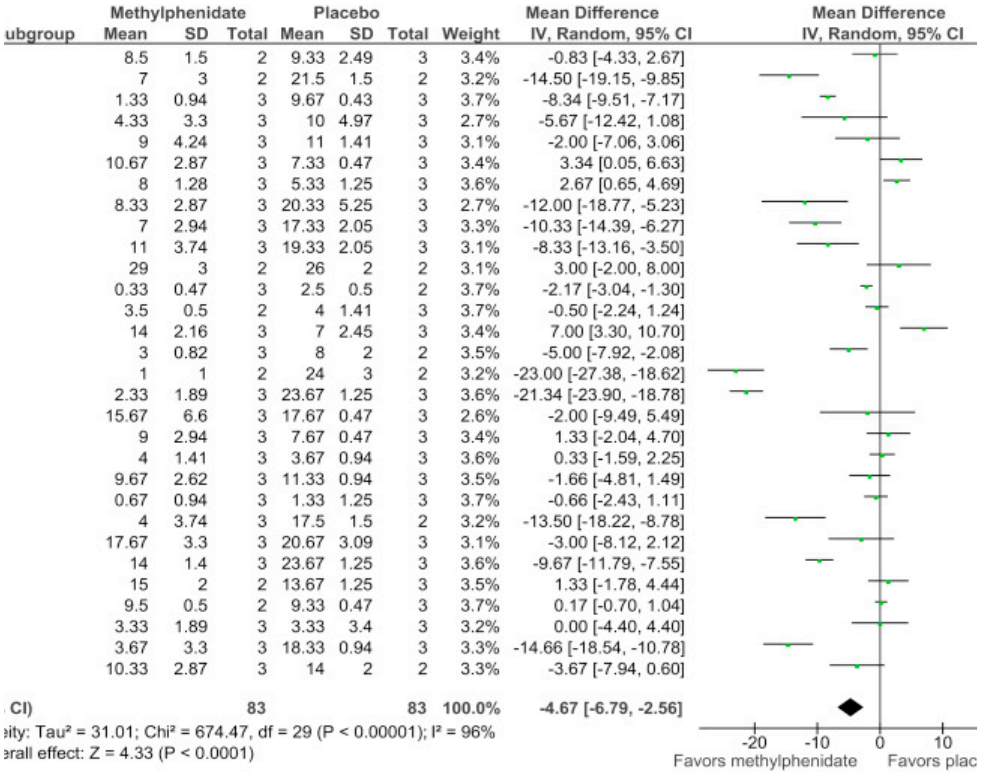
N-of-1 trials of methylphenidate vs. placebo



Punja et al. *J Clin Epidemiol*, 2016;76:65-75.

Meta-analysis

N-of-1 trials of methylphenidate vs. placebo

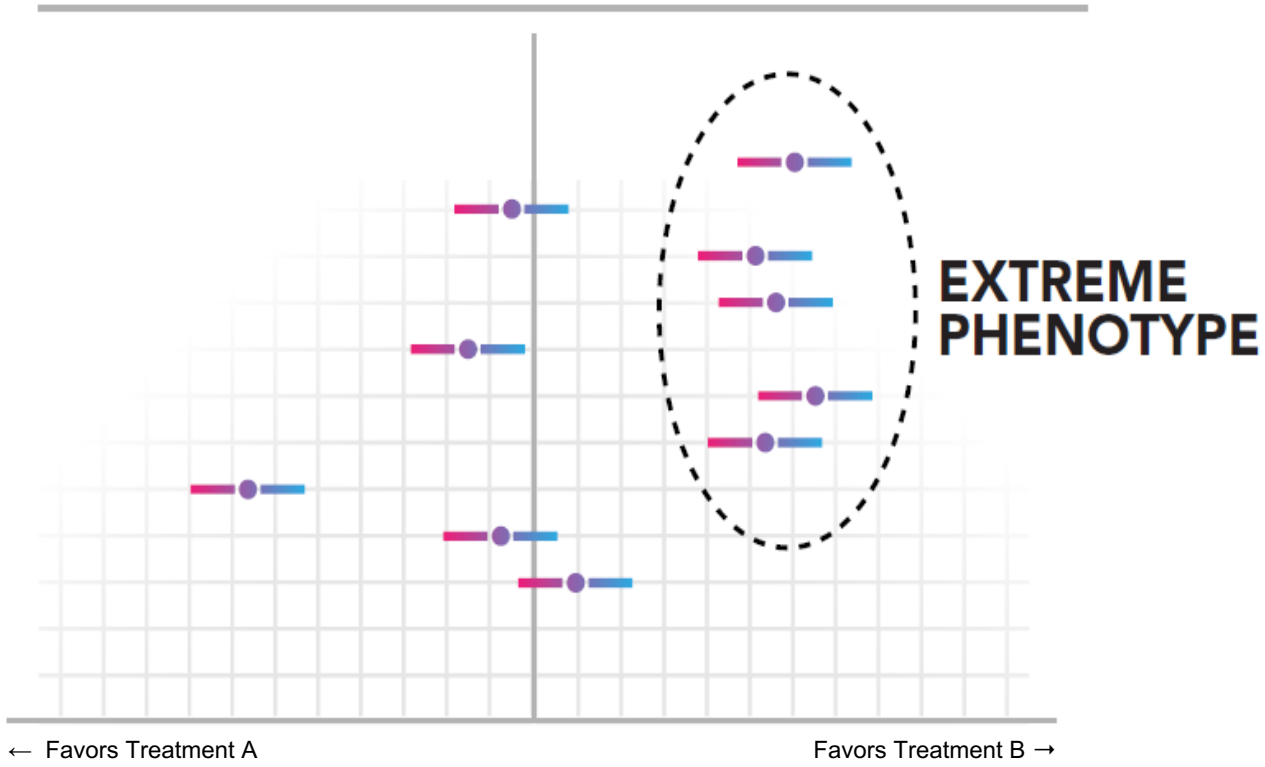


ubgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
	8.5	1.5	2	9.33	2.49	3	3.4%	-0.83 [-4.33, 2.67]
	7	3	2	21.5	1.5	2	3.2%	-14.50 [-19.15, -9.85]
	1.33	0.94	3	9.67	0.43	3	3.7%	-8.34 [-9.51, -7.17]
	4.33	3.3	3	10	4.97	3	2.7%	-5.67 [-12.42, 1.08]
	9	4.24	3	11	1.41	3	3.1%	-2.00 [-7.06, 3.06]
	10.67	2.87	3	7.33	0.47	3	3.4%	3.34 [0.05, 6.63]
	8	1.28	3	5.33	1.25	3	3.6%	2.67 [0.65, 4.69]
	8.33	2.87	3	20.33	5.25	3	2.7%	-12.00 [-18.77, -5.23]
	7	2.94	3	17.33	2.05	3	3.3%	-10.33 [-14.39, -6.27]
	11	3.74	3	19.33	2.05	3	3.1%	-8.33 [-13.16, -3.50]
	29	3	2	26	2	2	3.1%	3.00 [-2.00, 8.00]
	0.33	0.47	3	2.5	0.5	2	3.7%	-2.17 [-3.04, -1.30]
	3.5	0.5	2	4	1.41	3	3.7%	-0.50 [-2.24, 1.24]
	14	2.16	3	7	2.45	3	3.4%	7.00 [3.30, 10.70]
	3	0.82	3	8	2	2	3.5%	-5.00 [-7.92, -2.08]
	1	1	2	24	3	2	3.2%	-23.00 [-27.38, -18.62]
	2.33	1.89	3	23.67	1.25	3	3.6%	-21.34 [-23.90, -18.78]
	15.67	6.6	3	17.67	0.47	3	2.6%	-2.00 [-9.49, 5.49]
	9	2.94	3	7.67	0.47	3	3.4%	1.33 [-2.04, 4.70]
	4	1.41	3	3.67	0.94	3	3.6%	0.33 [-1.59, 2.25]
	9.67	2.62	3	11.33	0.94	3	3.5%	-1.66 [-4.81, 1.49]
	0.67	0.94	3	1.33	1.25	3	3.7%	-0.66 [-2.43, 1.11]
	4	3.74	3	17.5	1.5	2	3.2%	-13.50 [-18.22, -8.78]
	17.67	3.3	3	20.67	3.09	3	3.1%	-3.00 [-8.12, 2.12]
	14	1.4	3	23.67	1.25	3	3.6%	-9.67 [-11.79, -7.55]
	15	2	2	13.67	1.25	3	3.5%	1.33 [-1.78, 4.44]
	9.5	0.5	2	9.33	0.47	3	3.7%	0.17 [-0.70, 1.04]
	3.33	1.89	3	3.33	3.4	3	3.2%	0.00 [-4.40, 4.40]
	3.67	3.3	3	18.33	0.94	3	3.3%	-14.66 [-18.54, -10.78]
	10.33	2.87	3	14	2	2	3.3%	-3.67 [-7.94, 0.60]
CI)			83			83	100.0%	-4.67 [-6.79, -2.56]

ity: Tau² = 31.01; Chi² = 674.47, df = 29 (P < 0.00001); I² = 96%
erall effect: Z = 4.33 (P < 0.0001)

Punja et al. *J Clin Epidemiol*, 2016;76:65-75.

Registry N-of-1 Trials



Lanktree et al. *Cardiovasc* Genet, 2011; Hitunen et al. *JAHA*. 2015;

When are personalized trials appropriate?

Nature of the Disorder

Nature of the Treatment

Outcome Assessment

Stakeholders

Kravitz et al. AHRQ Evidence Synthesis, 2014

Case Study:

Designing a Prototype of N-of-1 Trials for Depressive Symptoms in Cancer Survivors

K. Davidson and I. Kronish, Co-Project Leaders

Nature of the disorder

Chronic stable

Slowly progressive

Frequently recurring

Nature of disorder:
Depressive symptoms in cancer survivors

Appropriate for N-of-1 trials if…		
Nature of the Disorder	✓	Subset with chronic stable or slowly changing depressive symptoms
Nature of the Treatment		
Availability of Outcome Assessment		
Willingness of Stakeholders		

Nature of the treatments

Uncertainty about best treatment option

Heterogeneity of treatment effects

Fast onset

Fast washout

*statistical methods can potentially account for washout

Nature of treatments:
Antidepressants, psychotherapy, CAM

Appropriate for N-of-1 trials if…	
Nature of the Disorder	✓ Subset with chronic stable symptoms
Nature of the Treatment	✓ Uncertainty about best treatment in cancer survivors ✓ Significant individual differences in treatment effects +/- Some treatments have rapid onset (e.g., light therapy) +/- Not all treatments sufficiently rapid & safe “washout”
Availability of Outcome Assessment	
Willingness of Stakeholders	

Availability of outcome assessments

Symptomatic conditions with valid, repeatable measures

Asymptomatic conditions with biomarkers

Availability of outcome assessments:
Questionnaires, psychiatric interviews

Appropriate for N-of-1 trials if…	
Nature of the Disorder	✓ Subset with chronic stable symptoms
Nature of the Treatment	✓ Uncertainty about best treatment ✓ Significant individual differences in treatment effects +/- Some treatments have rapid onset +/- Not all treatments sufficiently rapid & safe “washout”
Availability of Outcome Assessment	✓ Valid, repeatable measures of depressive symptoms and treatment side-effects
Willingness of Stakeholders	

Willingness of stakeholders

Patients, providers, and other stakeholders must be interested and engaged in such a trial

Willingness of Stakeholders:
Cancer survivors with depressive symptoms, clinicians

Appropriate for N-of-1 trials if…	
Nature of the Disorder	✓ Subset with chronic depressive symptoms
Nature of the Treatment	✓ Uncertainty about best treatment ✓ Significant individual differences in treatment effects +/- Some treatments have sufficiently rapid onset +/- Not all treatments sufficiently rapid & safe “washout”
Availability of Outcome Assessment	✓ Valid, repeatable measures of depressive symptoms and treatment side-effects
Willingness of Stakeholders	✓ Patients willing to use N-of-1 design to test CAM

Agenda

9:00 AM Welcome and introductions

9:15 AM How to decide if an N-of-1 trial design is right for you?

10:00 AM Breakout Session #1:
Discuss use cases for behavioral N-of-1 trials

10:30AM Coffee break 

10:45 AM How to design an N-of-1 trial protocol

11:30 AM The Science of Behavior Change (SOBC) Initiative

11:50 AM Wrap up discussion

Questions for Breakout #1

What are the best use cases for N-of-1 personalized trials?

When are personalized trials appropriate?

Nature of the Disorder	○ Chronic stable or ○ Slowly progressive or ○ Frequently recurring
Nature of the Treatment	○ Uncertainty about best treatment due to lack of evidence or large heterogeneity of treatment effects ○ Symptomatic conditions or asymptomatic conditions with biomarkers ○ Rapid onset and washout
Outcome Assessment	○ Validated, repeatable measures of treatment effects
Stakeholders	○ Patients, healthcare providers, health system willing to engage in N-of-1 trial effort

Kravitz et al. AHRQ Evidence Synthesis, 2014

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11:15 AM Breakout Session #2:
Design your own N-of-1 protocol

11:30 AM The Science of Behavior Change (SOBC) Initiative

11:50 AM Wrap up discussion

10:30AM Coffee break

Resume at 10:45AM

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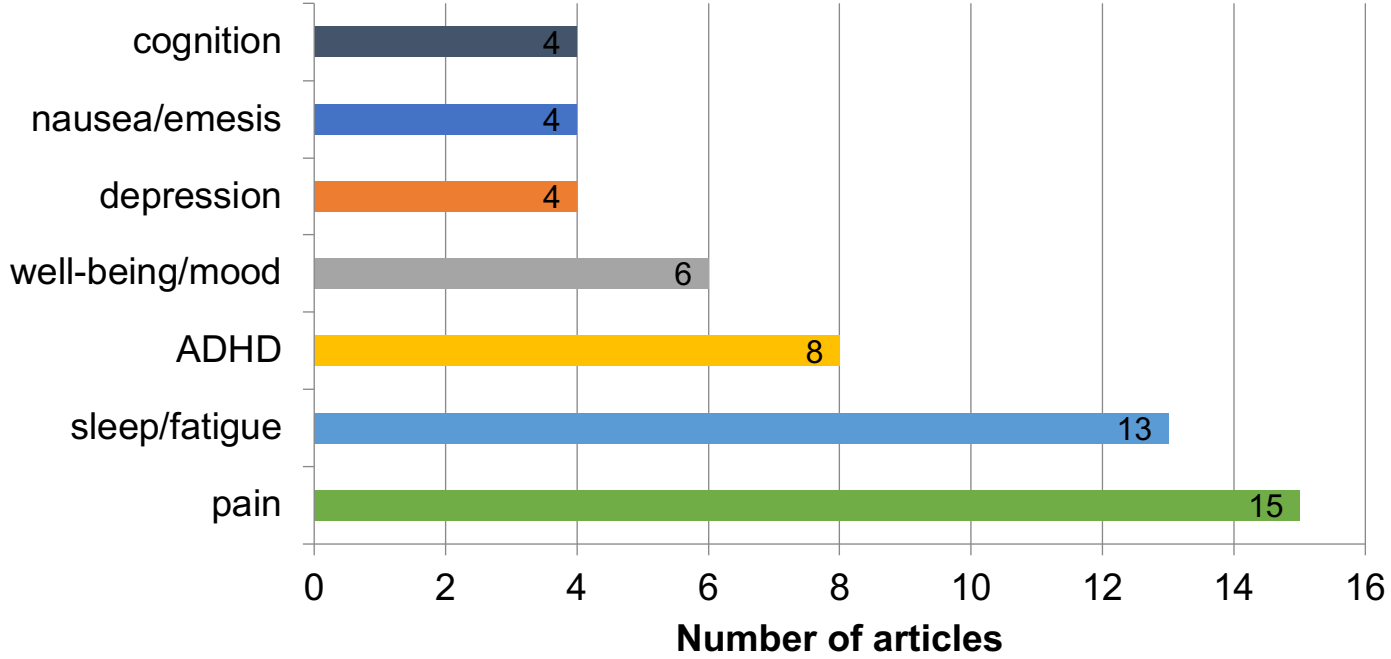
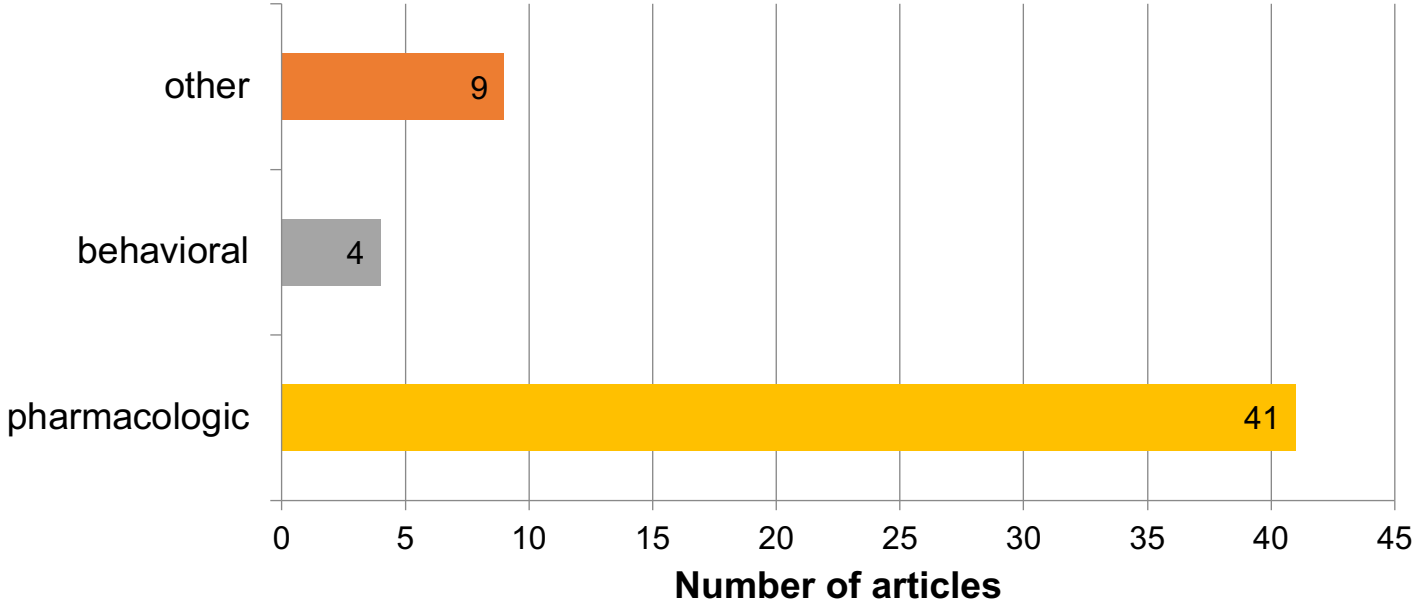
Types of conditions in published behavioral N-of-1 trials



Shaffer et al. Ann Behav Med. 2017

Types of interventions in published behavioral N-of-1 trials



Shaffer et al. Ann Behav Med. 2017

Behavioral interventions in N-of-1 trials

Behavioral self-control v methylphenidate for ADHD

(Anderson, Clement & Oettinger, *J Develop Behav Pediatr,* 1981)

Behavior modification v methylphenidate for ADHD

(Pelham et al. *J Consult Clin Psychol*,1983)

Goal setting v self-monitoring for walking

(Sniehotta et al. *Health Psychol*, 2012; Nyman et al. *Psychol & Health,* 2015)

A brief history of N-of-1 trials

1986

Guyatt et al.
"Determining optimal therapy" NEJM

1990

Larson launches grant-funded N-of-1 service at UW

34 N-of-1 trials over 2 years
85% of physicians would refer again; 79% of patients found useful

1992

N-of-1 service folds after grant funding expires

Cost ~$500 per N-of-1 trial; ~17 staff hours/trial

"The question really is – how many patients are there that really want to know this? And how many doctors are there…to promote this to patients. There are an awful lot of people who just want you to tell them what to take, and they'll do it."

“Market research”

Engaging Stakeholders in Building Patient-centered, N-of-1 Randomized and Other Controlled Trial Methods

(K. Davidson, PI)

Focus Groups

- 54 patients with 2+ conditions
- 24 primary care providers

National Poll

- 500 patients with 2+ conditions

pcori®

Key questions

① What are the perceived benefits and barriers to N-of-1 trials?

② Which conditions, diseases, symptoms and/or treatments are amenable to N-of-1 trials?

③ What design decisions must be made to increase the acceptability and sustainability of N-of-1 trials?

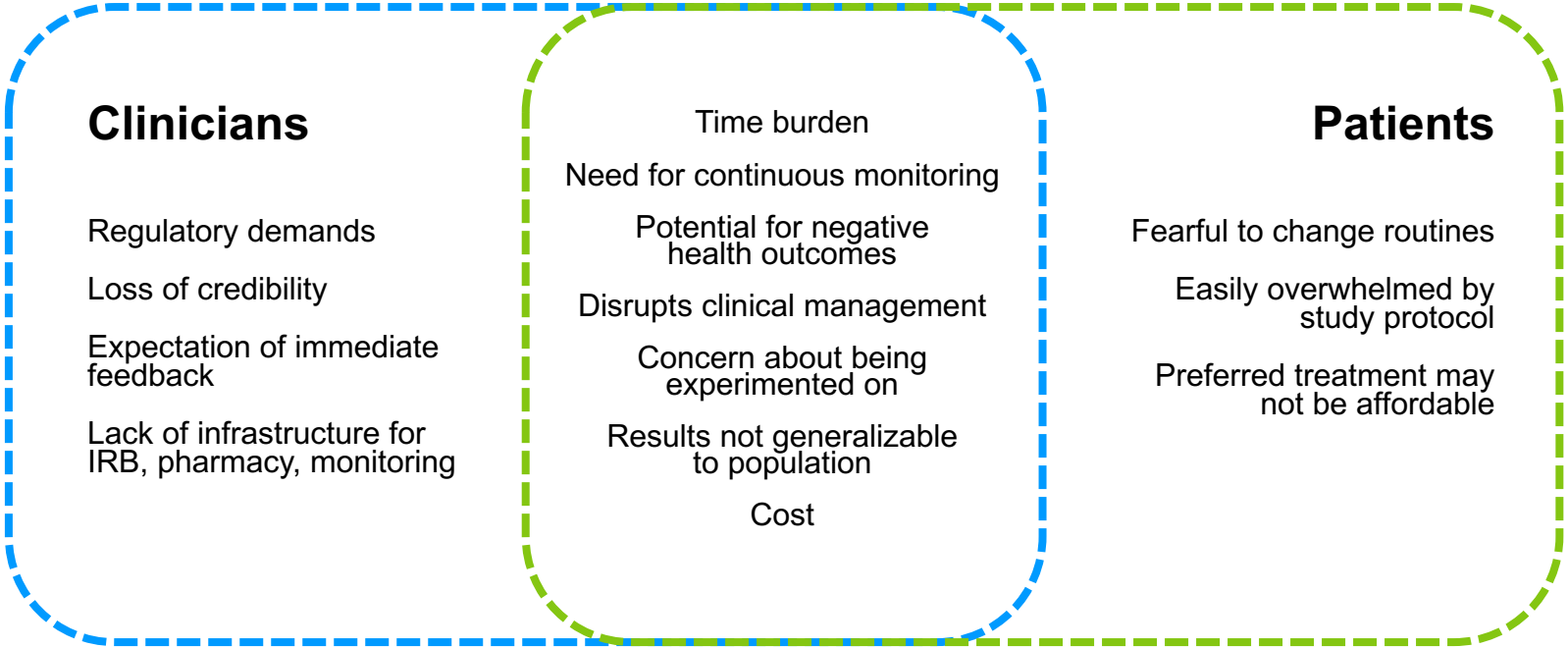
Perceived benefits

"I kind of like that approach because I think it would empower me to really sense how the treatment is affecting my body. And I think that would be very beneficial, being responsible for my own health"

-Patient D, 5.04.15

Medical care	Identifies best treatments for individual patients Participation results in direct health benefit Results are immediately known
Clinician-patient relationship	Facilitates communication Validates patient feedback Makes patients feel uniquely cared for
Patient engagement in care	Increases knowledge of own condition, treatment and treatment side-effects Increases sense of autonomy
Opportunity to participate in research	Customized inclusion criteria Geographic availability Promotes science to benefit self and community

Perceived concerns of N-of-1 Trials



Ideal conditions: focus groups

Clinicians

- **Hypertension**
- **Depression**
- Seizures
- Dementia
- Acid reflux
- Allergies
- Migraines
- Oral contraceptives
- Asthma
- Hyperlipidemia
- Generic vs. trade name
- Remedy for non-compliance
- Treatment requires titrations
- Medications with short half-life
- Good outcome measures
- Safe to switch medications
- Several treatment options
- High stakes/hard to control
- Expensive treatment options

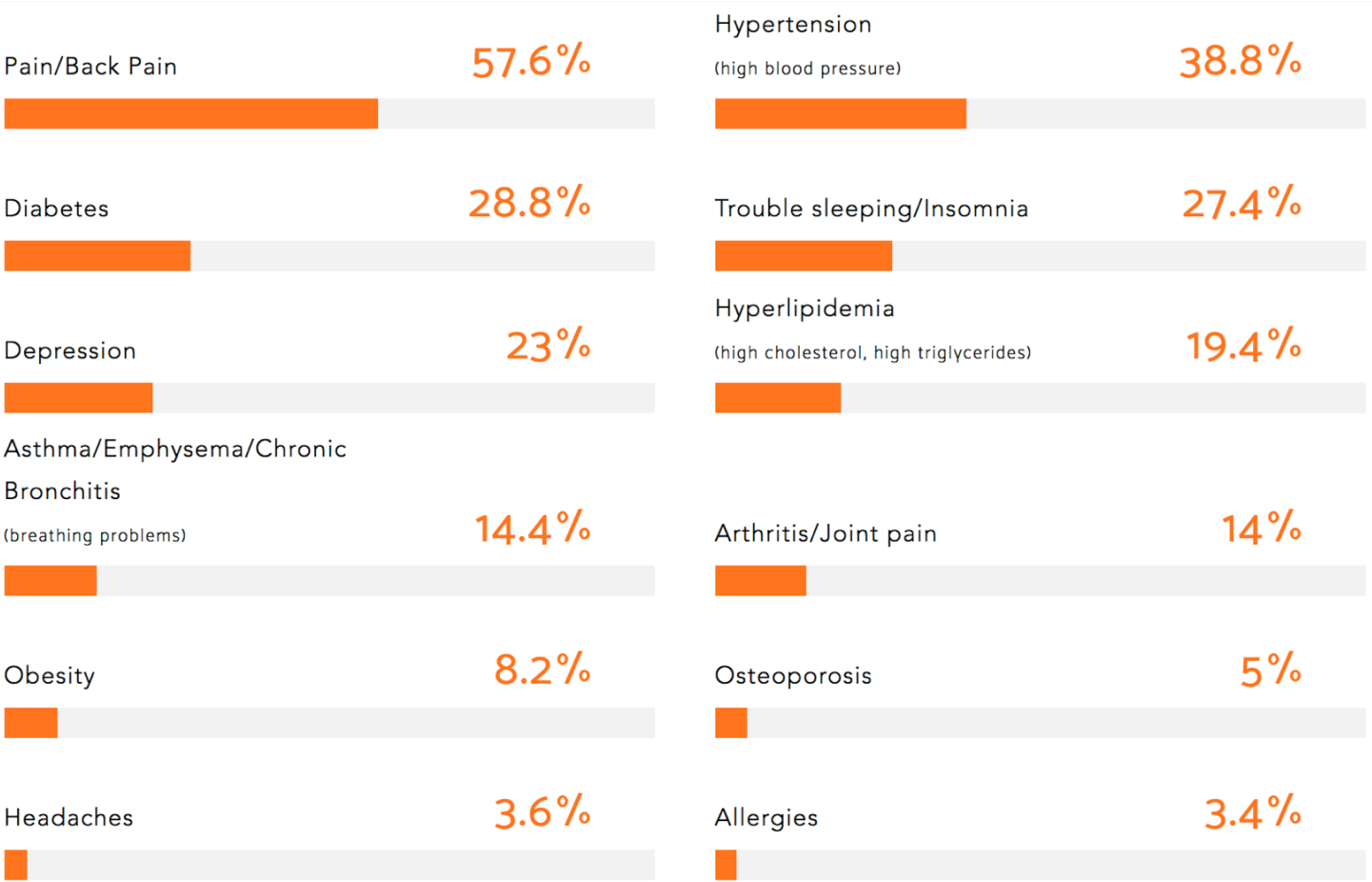
Clinicians & Patients

- Chronic pain
- Diabetes
- Arthritis
- Medication side effects

Patients

- COPD
- IBS
- Parkinson’s
- Shortness of Breath
- Cancer

Ideal conditions: national poll



How to design an N-of-1 Trial

Determine whether N-of-1 methodology is applicable to the question

Select sequence: treatment period length and sequencing scheme (e.g., ABAB)

Invoke a suitable washout period

Decide whether or not to invoke blinding

Select suitable outcomes domains and measures

Analyze and present data

Other considerations

Ethical framework: clinical care vs. research vs. both

Financing

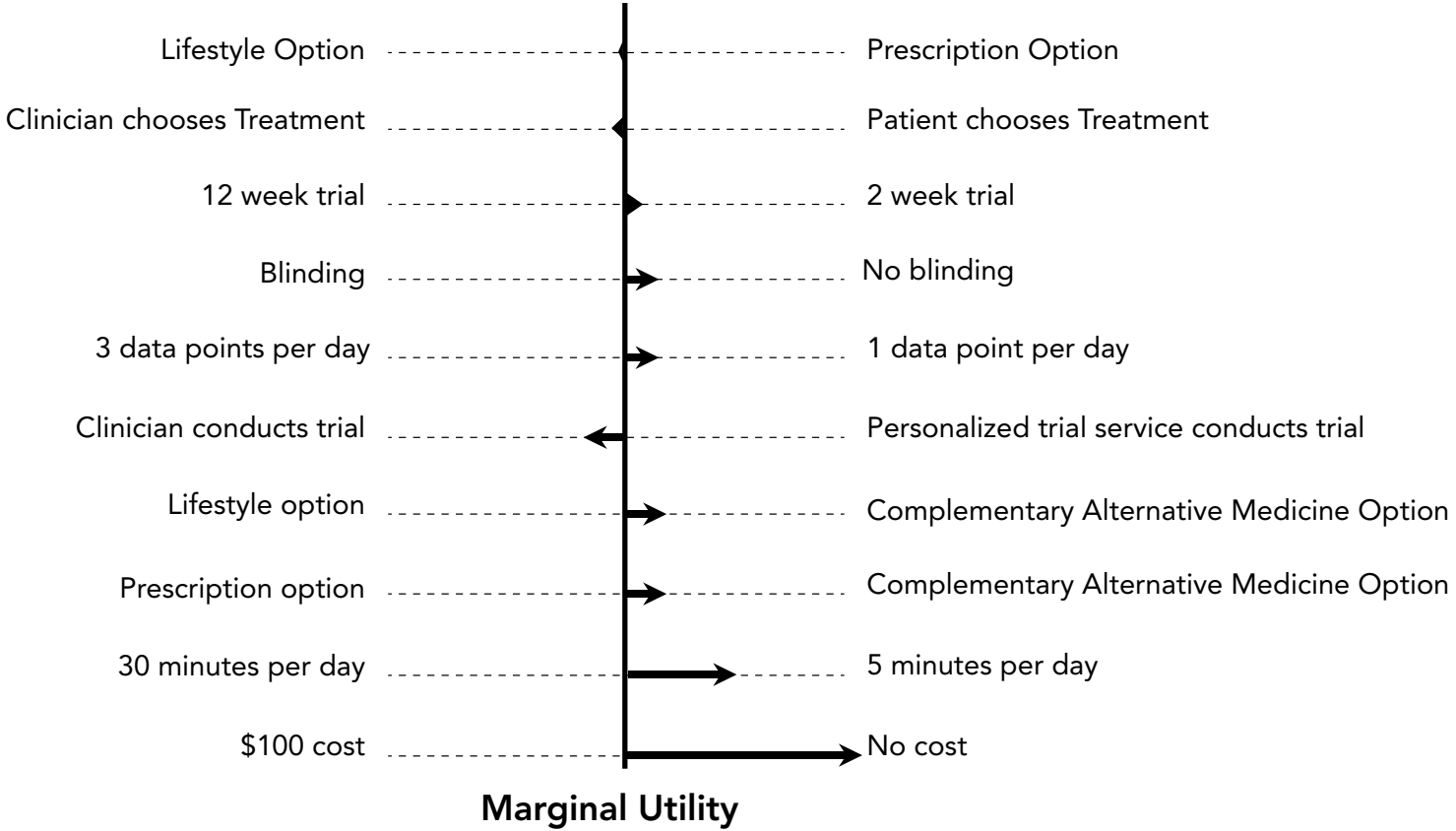
Information technology infrastructure

User engagement, training, and support

Which design feature(s) are most important?

Lifestyle Option	Prescription Option
Clinician chooses Treatment	Patient chooses Treatment
12 week trial	2 week trial
Blinding	No blinding
3 data points per day	1 data point per day
Clinician conducts trial	Personalized trial service conducts trial
Lifestyle option	Complementary Alternative Medicine Option
Prescription option	Complementary Alternative Medicine Option
30 minutes per day	5 minutes per day
$100 cost	No cost

Which design feature(s) are most important?



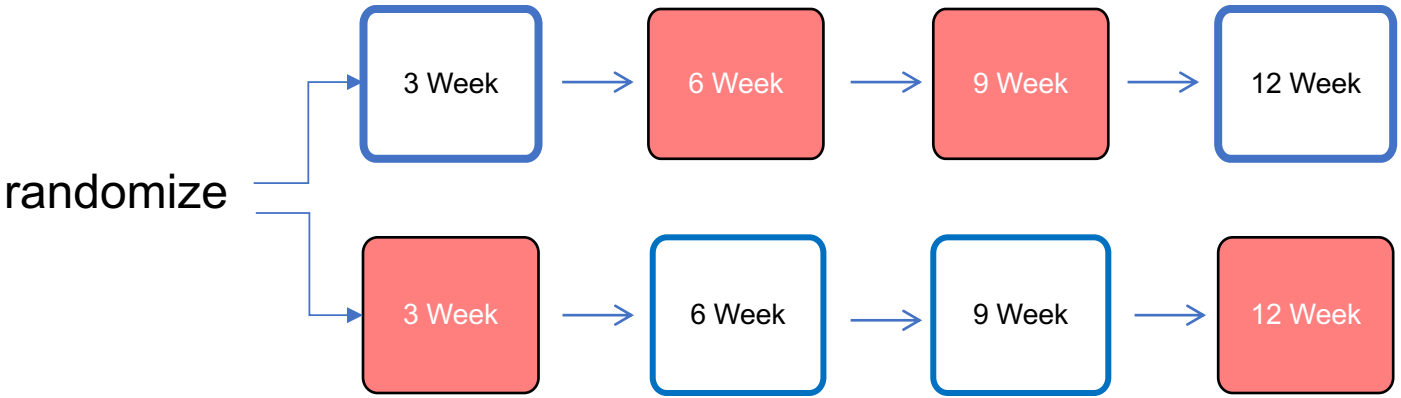
Case Study

DJ is a 62 year-old male with fatigue and depressive symptoms after prostate cancer diagnosis

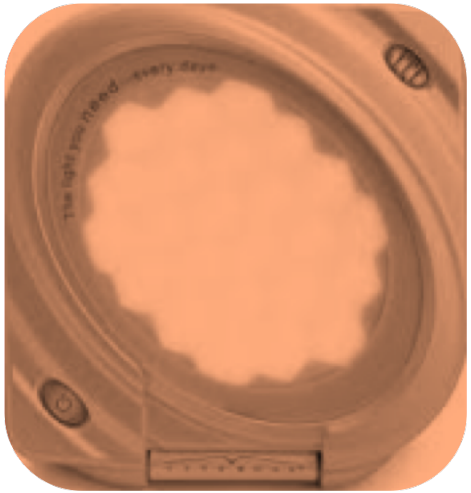
He is concerned about side-effects from treatment and wants to be on the least amount of medication

He wonders whether light therapy will be helpful for him

Select sequence, washout period



Decide on blinding / masking



Select outcomes

STEP 1 OF 3

How tired or fatigued are you feeling right now?

5

0 — 10

NOT AT ALL TIRED — EXTREMELY TIRED

Next

STEP 2 OF 3

How sad or depressed are you feeling right now?

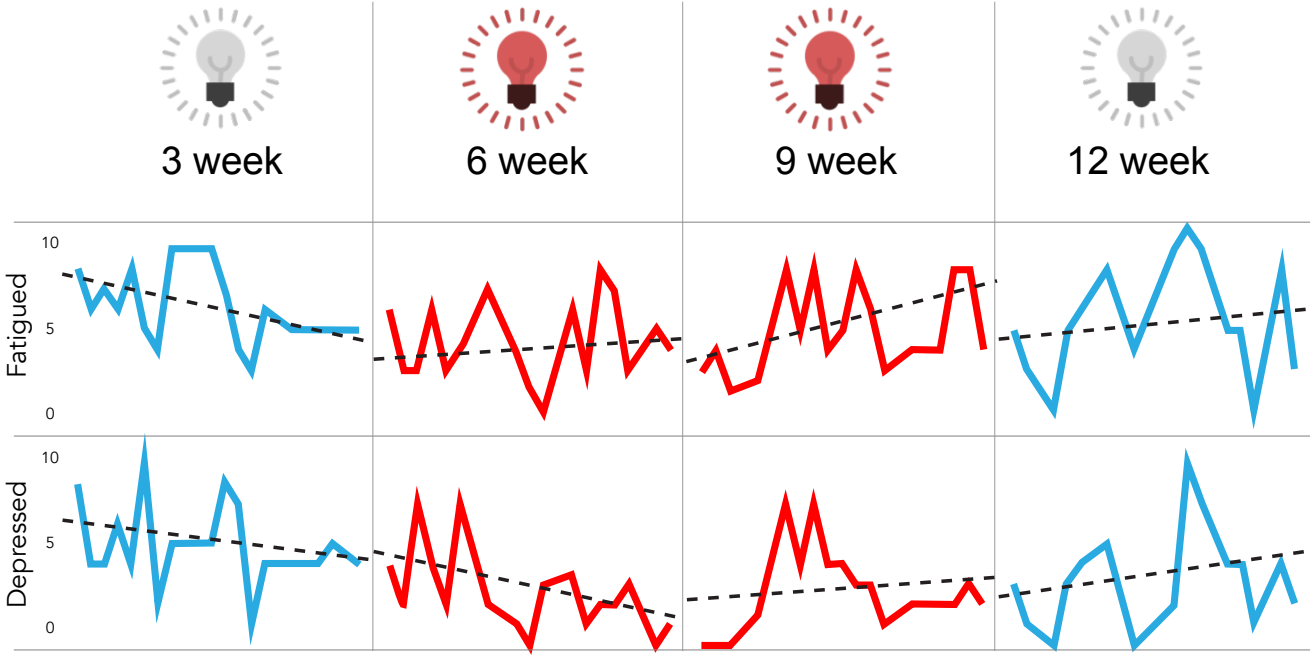
5

0 — 10

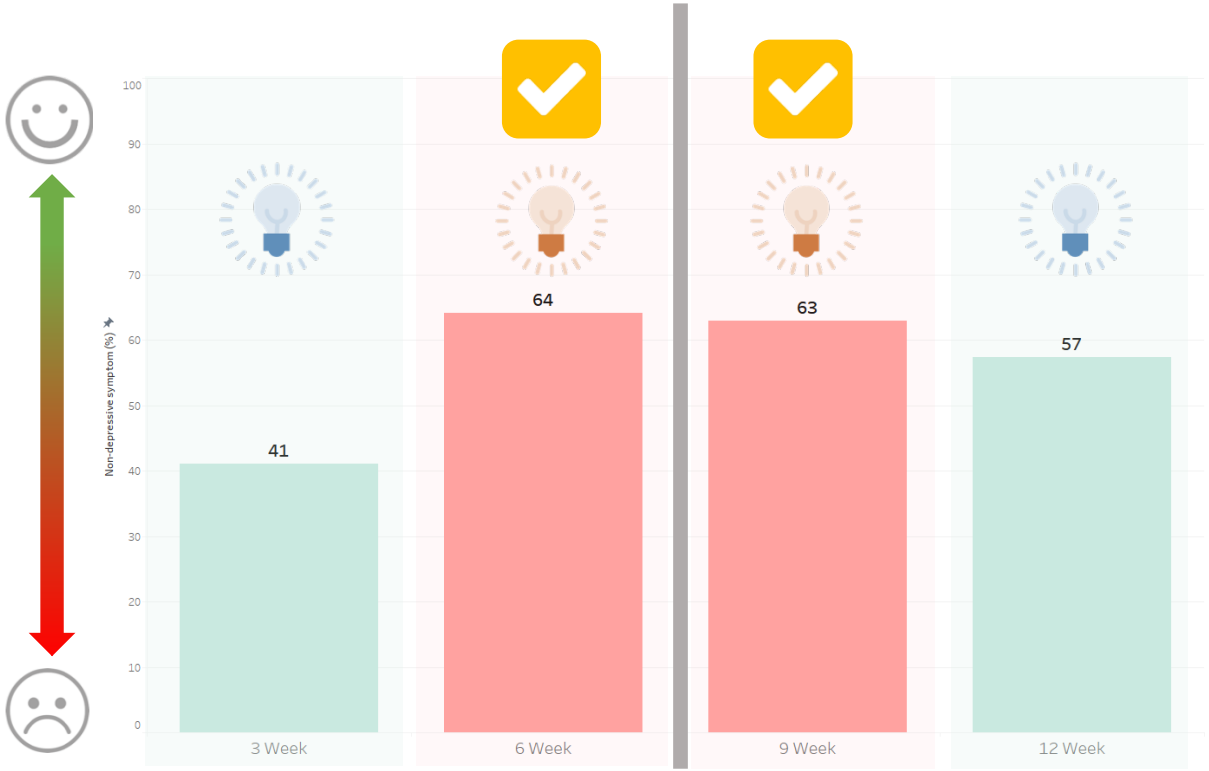
NOT AT ALL DEPRESSED — EXTREMELY DEPRESSED

Next

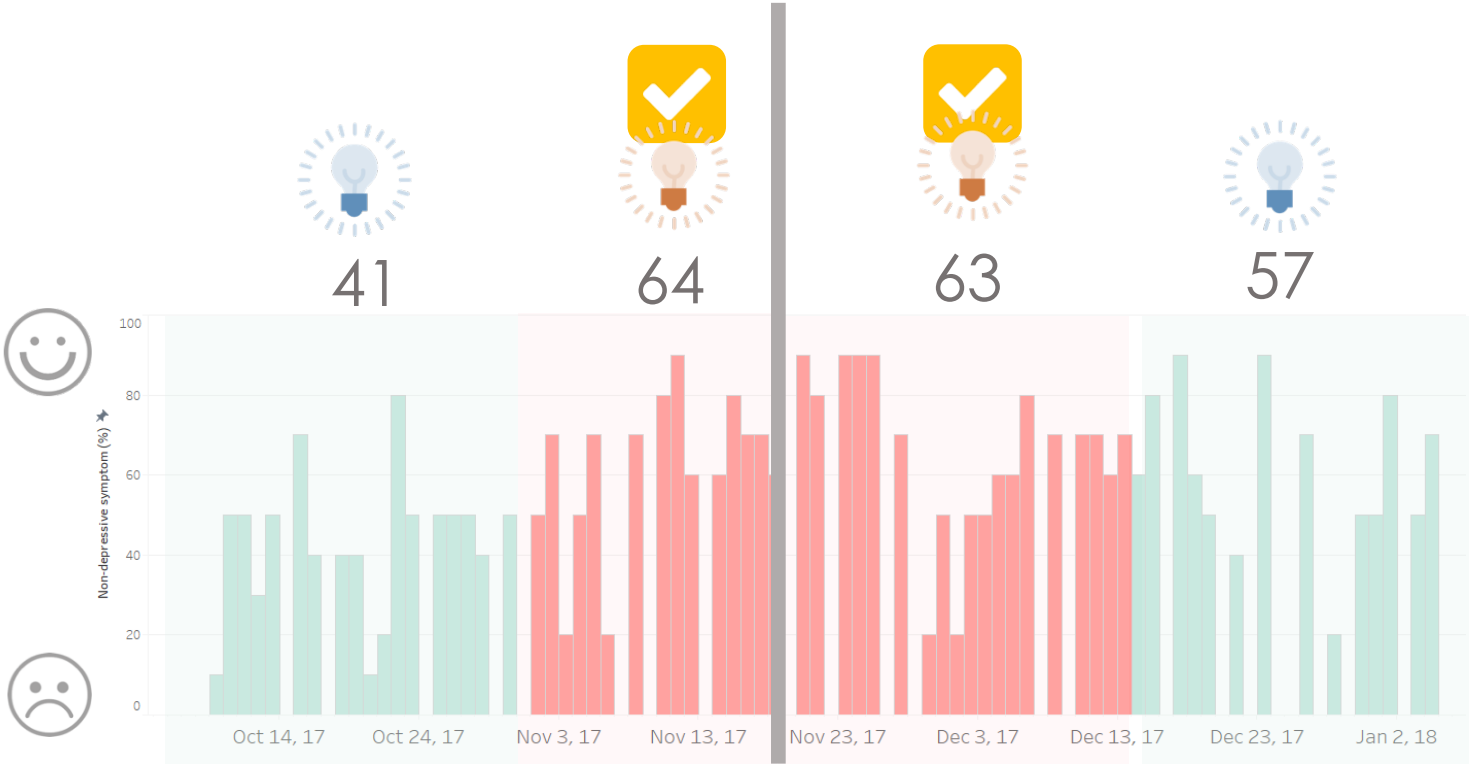
Analyze and present results



Analyze and present results



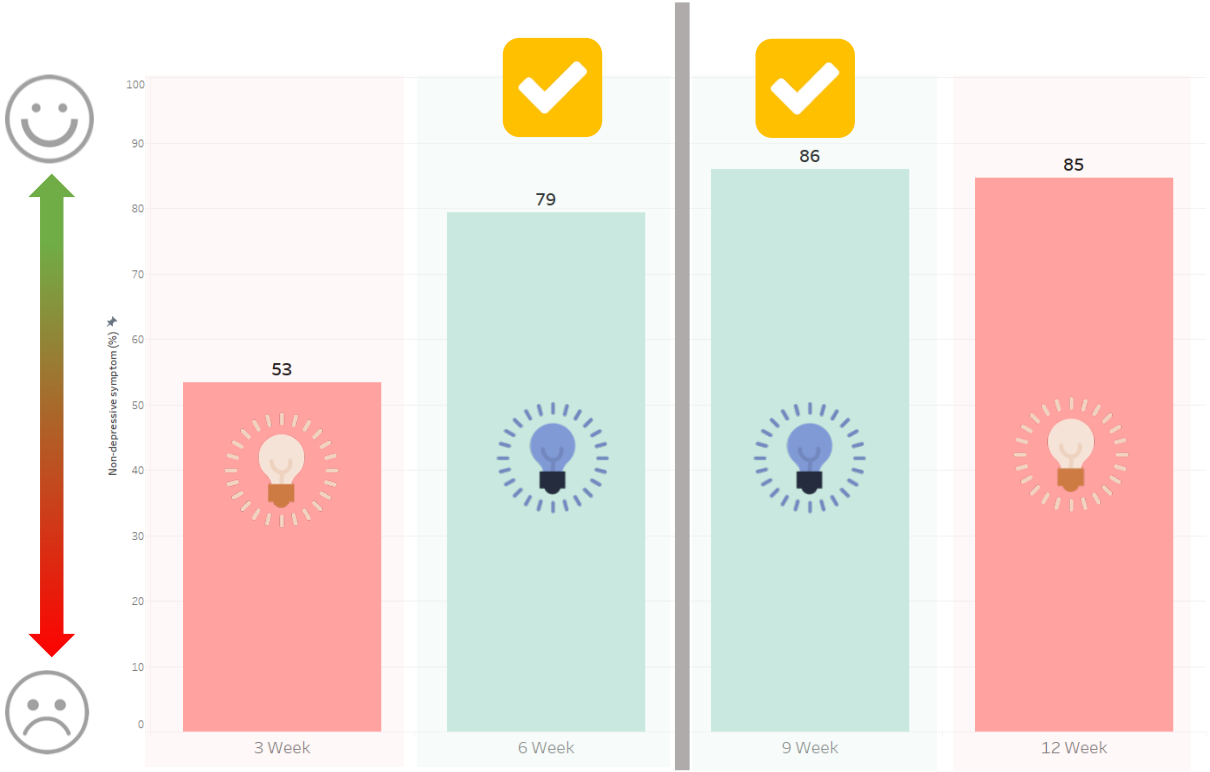
Analyze and present results



Analytic approach

	Model 1: Regression	Model 2: Regression adjusted for linear time trend	Model 3: Regression adjusted for auto-correction	Model 4: Regression adjusted for auto-correction and linear time trends
Difference in Mood VAS score: Red v Bright White (range: 0-10)	-1.53 p=0.004	-1.43 p=0.006	-1.50 p=0.02	-1.41 p=0.03
Linear trend	-	-0.48 p=0.04	-	-0.49 p=0.08
Auto-correction*	-	-	0.24	0.21

Analyze and present results



Other considerations

Ethical framework: clinical and research

Financing: via grants

IT Infrastructure: iPhone app

User engagement, training & support: conducted by study team

Personalizedtrials.org

personalized trials n=1

Home | What is Personalized Trials? | How to Get Involved | About | For Researchers

Personalized Trials is a different way to think about health care.

Not everybody responds to treatment the same way. Personalized Trials gives you the tools to find the treatment that's right for you.

Agenda

9:00 AM Welcome and introductions

9:15 AM How to decide if an N-of-1 trial design is right for you?

10:00 AM Breakout Session #1:
Discuss use cases for behavioral N-of-1 trials

10:30AM Coffee break 

10:45 AM Designing an N-of-1 trial protocol

11:30 AM The Science of Behavior Change (SOBC) Initiative

11:50 AM Wrap up discussion

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Bringing an Experimental Medicine Approach to Behavior Change Research:

The NIH Science Of Behavior Change Program

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Behaviors are among the most important factors that determine whether people will live long, healthy lives.

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Chronic diseases contribute to 7 out of 10 deaths in the U.S.
Treatment of these diseases accounts for over 85% of U.S. health costs.
Many of these chronic diseases are preventable.

accounts for almost 40% of the risk associated with preventable premature deaths in the U.S.

The Power of Prevention: Chronic Disease...The Public Health Challenge of the 21st Century. Atlanta, GA: Centers for Disease Control and Prevention; 2009.
Yoon PW, Bastian B, Anderson RN, Collins JL, Jaffe HW. Potentially preventable deaths from the five leading causes of death—United States, 2008–2010. Morbidity and Mortality Weekly Report 2014; 63(17): 369-74.

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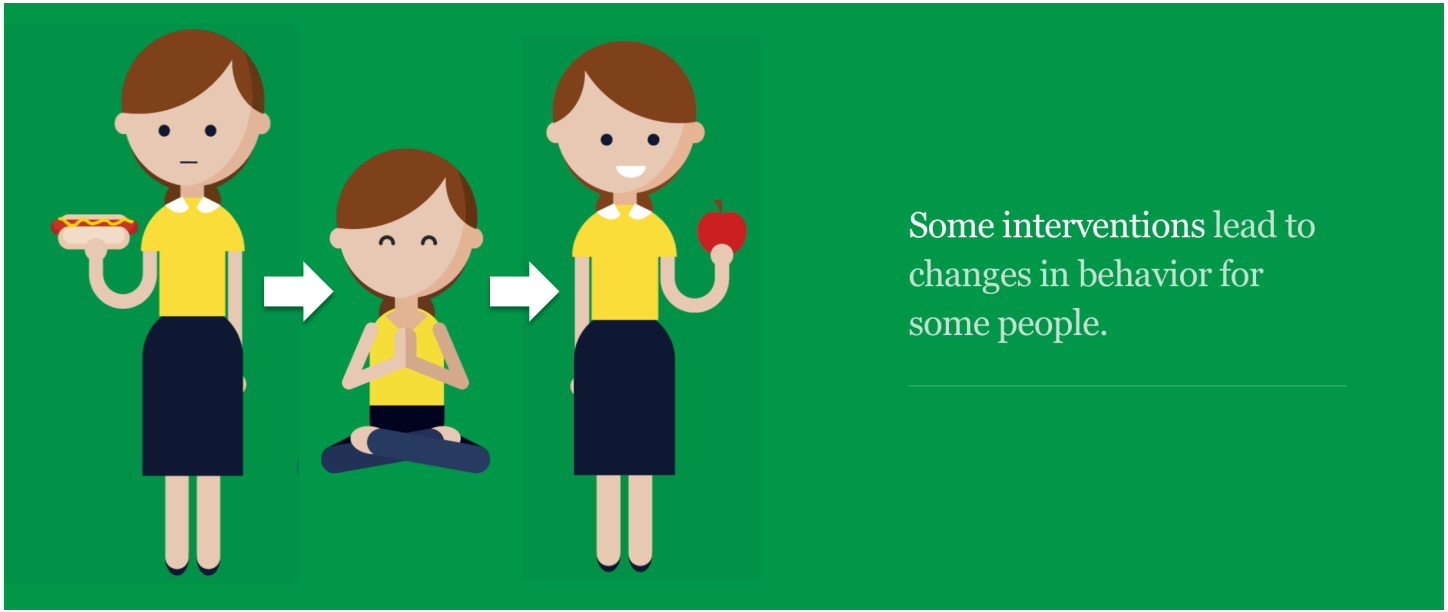

Some interventions lead to changes in behavior for some people.

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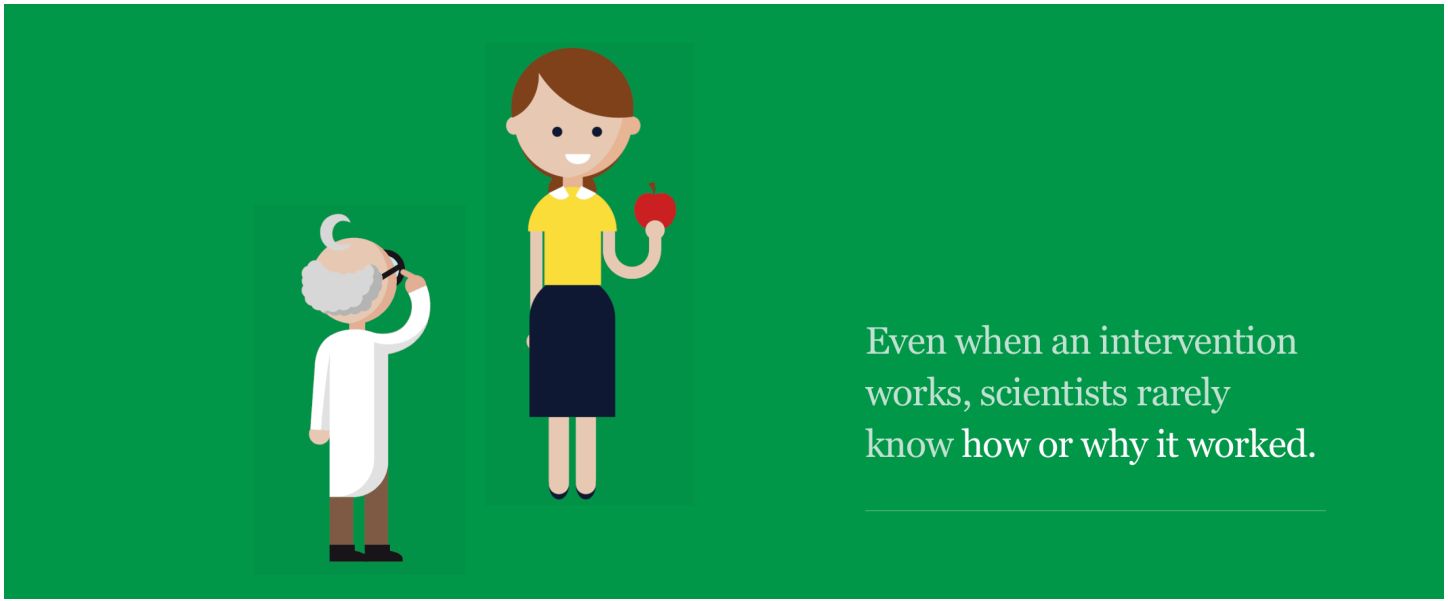

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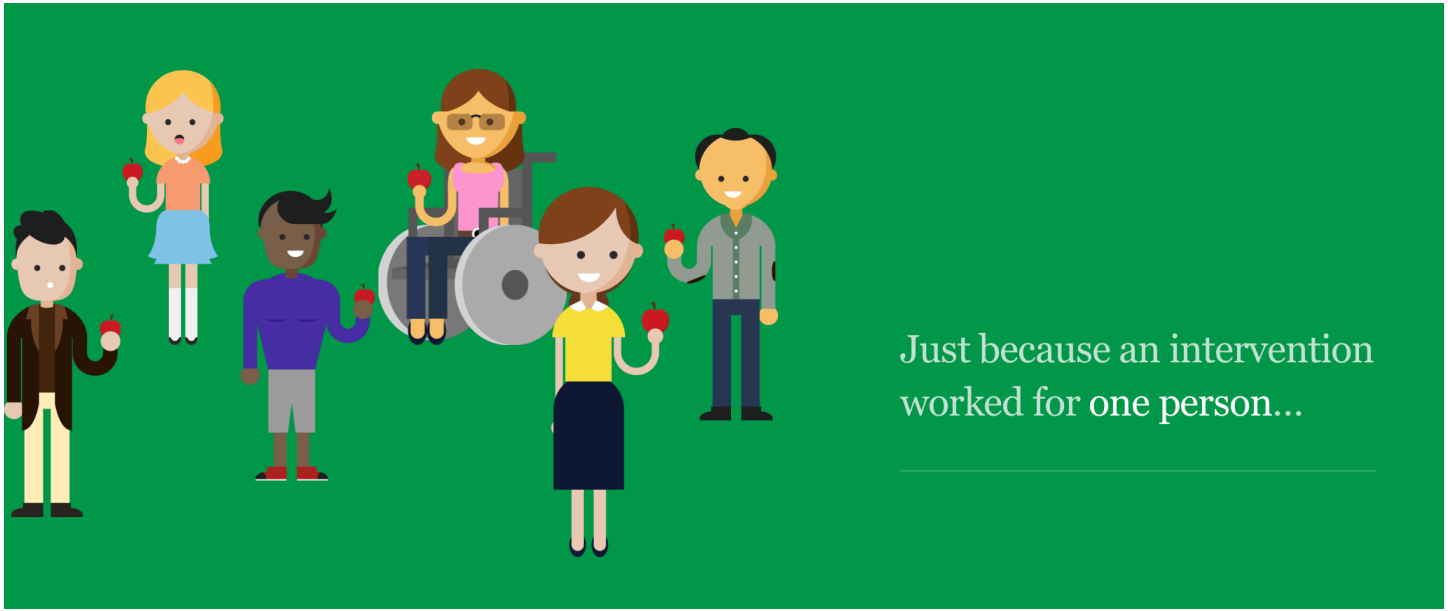

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doesn't mean it will work for another.

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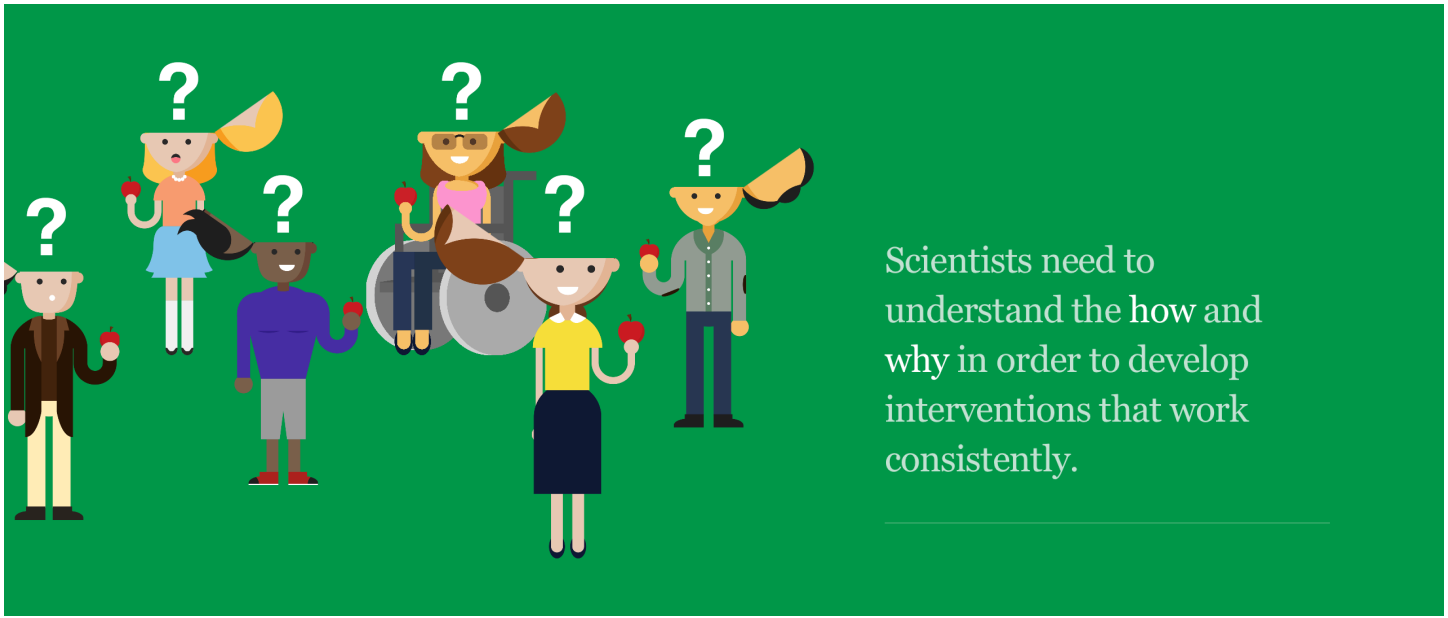

Scientists need to understand the **how** and **why** in order to develop interventions that work consistently.

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If you've ever wondered why it's so hard to stick to that diet or exercise routine, researchers at Science Of Behavior Change are wondering that too.

A lot of work has been done in the field of behavioral medicine in order to help people make healthy choices, and some of that work has been successful. The problem is that even when these efforts are successful, we don't know why or how they worked. Understanding why successful behavior change occurs is the key to getting it to happen again.

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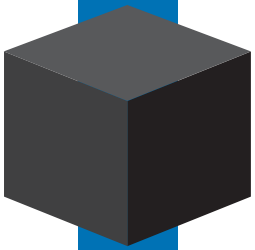
HEALTH BEHAVIOR

INTERVENTION



CHANGE IN BEHAVIOR

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A New Way Forward

Focus on mechanisms of change

Develop and apply a common and transparent scientific method

Optimize interventions to promote effectiveness by targeting mechanisms

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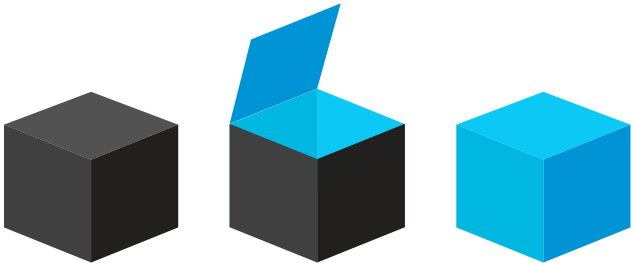
The Method and the Measures



A Common Method

for understanding behavior change.

Experimental Medicine Approach

Aims to identify key mechanisms underlying successful behavior change

Offers intermediate targets on the causal path to behavior change

Helps us understand why an intervention worked or didn't work


SO
BC
Science
Of
Behavior
Change
Experimental
Medicine
Approach
Identify
Mechanism
Measure
Mechanism
Influence
Mechanism
MECHANISM
CHANGE
BEHAVIOR
CHANGE

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Validating Measures with the Method

Measures Repository

Developing a repository of validated measures

- Progress through steps of the method
- Open Science Framework (OSF) documentation
- 113 measures…and more to come!

Resource for the scientific community

www.scienceofbehaviorchange.org/measures

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Validation Process

Measure Progress Bar

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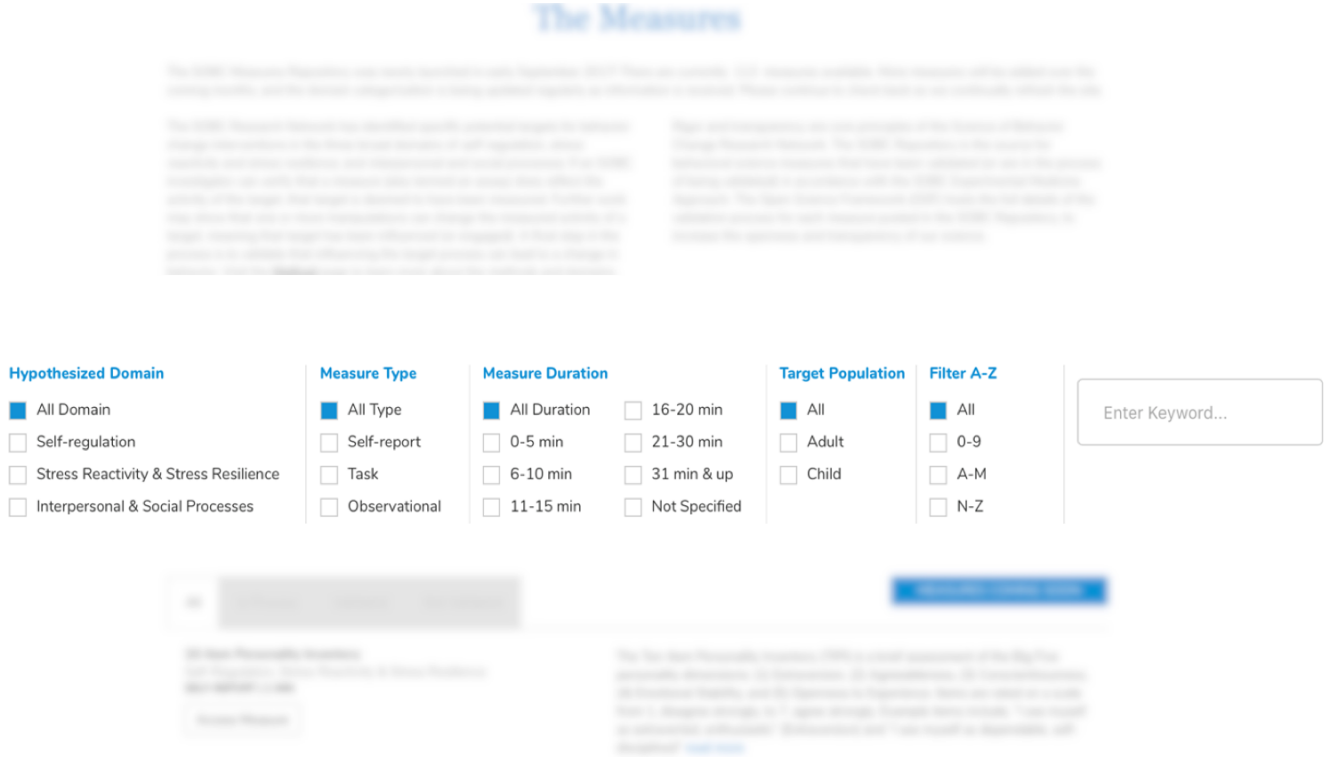
Access the Measures



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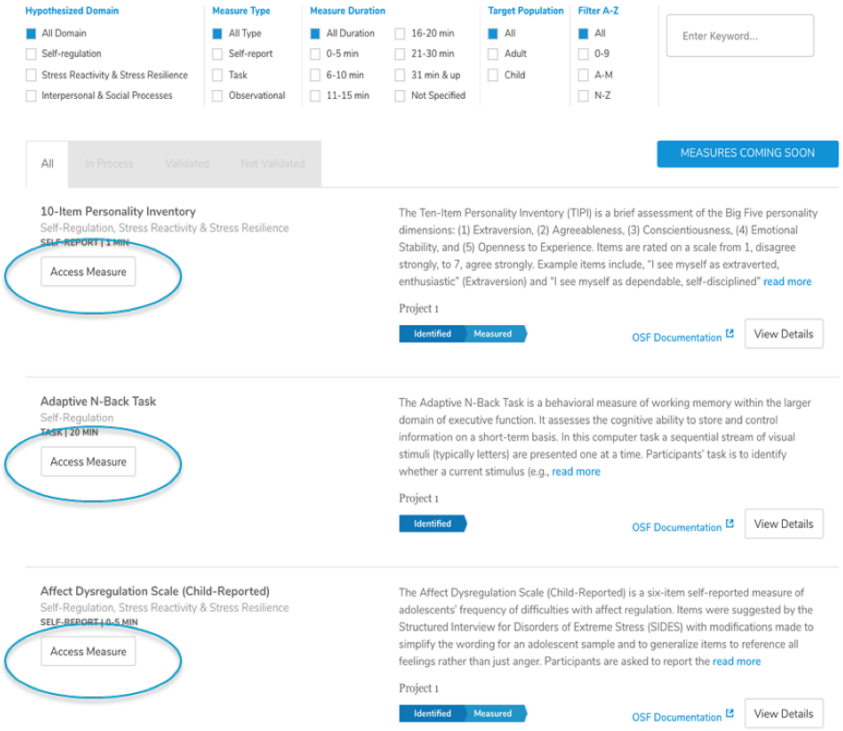
Access the Measures



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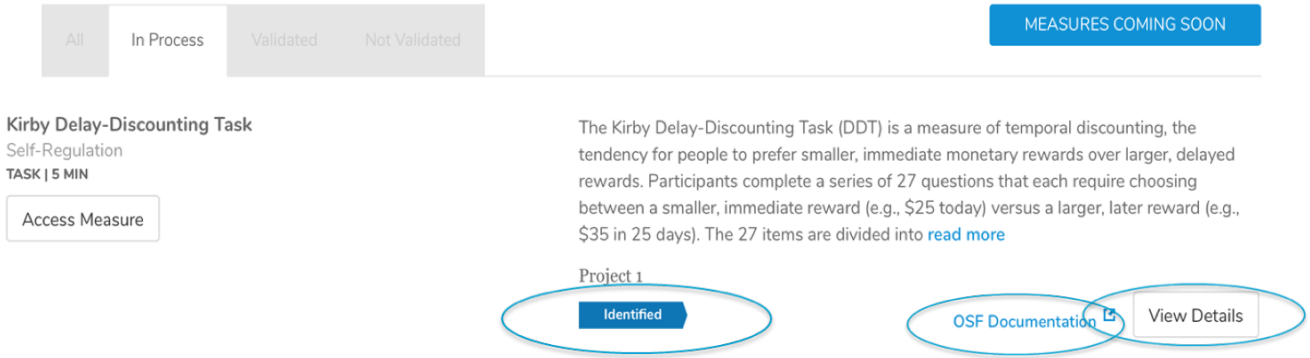

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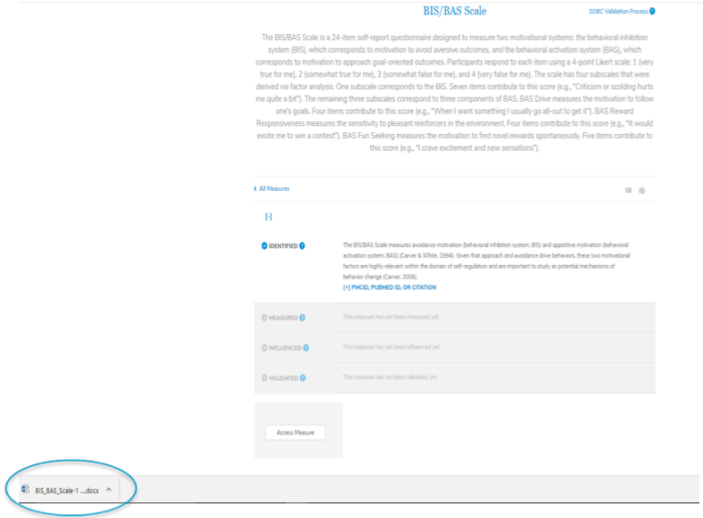

BIS/BAS Scale:

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Choose only one response to each statement.

	Very true for me	Somewhat true for me	Somewhat false for me	Very false for me
1. A person's family is the most important thing in life.	☐	☐	☐	☐
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness.	☐	☐	☐	☐
3. I go out of my way to get things I want.	☐	☐	☐	☐
4. When I am doing well at something I love to keep at it.	☐	☐	☐	☐
5. I am always willing to try something new if I think it will be fun.	☐	☐	☐	☐
6. How I dress is important to me	☐	☐	☐	☐
7. When I get something I want, I feel excited and energized.	☐	☐	☐	☐
8. Criticism or scolding hurts me quite a bit.	☐	☐	☐	☐
9. When I want something I usually go all-out to get it.	☐	☐	☐	☐
10. I will often do things for no other reason than that they might be fun.	☐	☐	☐	☐

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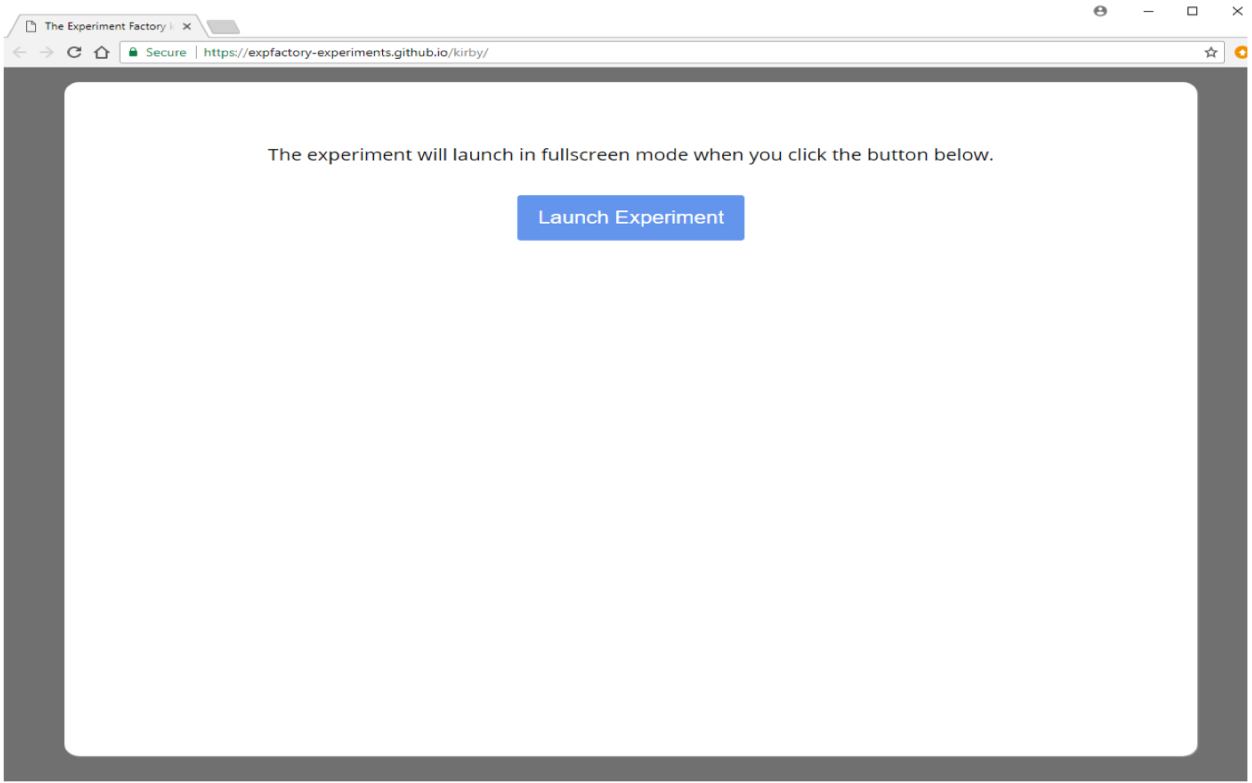
Access the Measures



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SOBC/Experimental medicine approach

1. Hypothesize mechanisms first
2. Determine whether you can measure them
3. Determine whether you can influence them
4. Determine whether changing them can change behavior
5. Test an intervention optimized to change them, and thereby change behavior

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Visit us at:

scienceofbehaviorchange.org

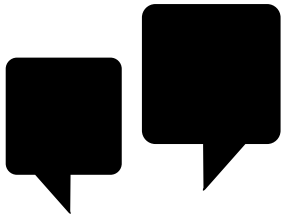
Summary

N-of-1 trials can provide knowledge about the benefits and harms to the individual

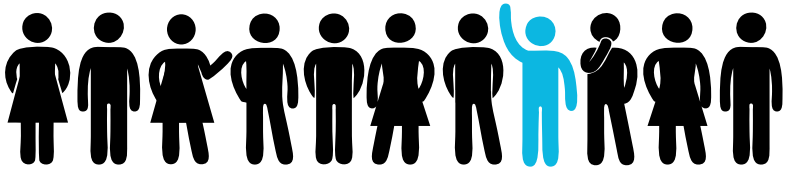
May result in more precise regimen, higher satisfaction, better adherence, better health outcome

Pooling data provides opportunity for generalizable knowledge

N-of-1 observational studies can be used to identify personal predictors and triggers



Discussion & Wrap-Up



International Behavioral Trials Network
May 24, 2018, Montreal, Canada
Karina Davidson, PhD & Ian Kronish, MD, MPH

Thank you.