

INTRODUCTION

Using Early Phase Studies to Advance Intervention Research: The Science of Behavior Change

Karina W. Davidson and Jazmin N. Mogavero
Northwell Health, New York, New York

Alexander J. Rothman
University of Minnesota

This special issue showcases how investigators working in different areas of health behavior change are utilizing early phase studies to advance intervention development. Through the publication of design or protocol papers for currently funded Science of Behavior Change (SOBC) network projects, the special issue illustrates how investigative teams are implementing the experimental medicine approach to advance our understanding of the mechanisms of action that underlie behavior change interventions and, in turn, develop an evidence base that can inform future intervention design. Given that a goal of the experimental medicine approach is the accumulation of an evidence base regarding the links between intervention strategies and putative mechanisms of action, it is critical that this evidence base is readily accessible to investigators and practitioners. Therefore, each of the included articles describes how it is implementing the open-science approach within its study protocol to ensure rigor and reproducibility. Each article provides information about how to register an early phase experiment before study conduct and how to publicly deposit the data, metadata, and publications. The special issue includes 10 design and protocol articles and 2 commentaries on a diverse array of scientific areas and approaches to test mechanisms of action for health behavior change interventions. By disseminating how the National Institutes of Health SOBC Initiative has supported the conduct of early phase intervention studies implementing the experimental medicine and open science approaches, the special issue provides a substantive roadmap to other scientists for how to adopt these approaches.



Keywords: science of behavior change, mechanisms of action, experimental method, early phase study design, open science

Interventions that can effectively and efficiently elicit changes in people's health behavior are a primary focus of research in health psychology and behavioral medicine. Journals are replete

with reports of trials that test the impact of innovative intervention strategies on behaviors ranging from eating and exercise to adherence to treatment and screening protocols. Although our research and publication practices focus on the outcomes generated by these trials, there is a growing recognition that their informational value critically depends upon how investigators conduct the preliminary studies that underlie the development of the intervention (Czajkowski et al., 2015; Freedland, 2019). Yet, these preliminary studies are frequently not reported.

In many ways, the conception, design, and conduct of studies in the early phase of research programs are the Achilles heel of most initiatives to promote health behavior change. Traditionally, these studies have been characterized as feasibility and pilot studies, with a focus on addressing questions regarding how and whether a randomized controlled trial (RCT) evaluating the efficacy of an intervention can and should be conducted (Eldridge et al., 2016). Although the value of pilot studies that are conceptualized as "preliminary efficacy trials" is uncertain at best (Freedland, 2020), investigators can utilize early phase studies to generate evidence that provides the foundation on which an intervention trial rests. In particular, early phase studies provide investigators with the opportunity to specify the constructs an intervention should target, to refine or develop methods for assessing changes in those con-

Editor's Note. This is an introduction to the special issue "The Science of Behavior Change: Implementing the Experimental Medicine Approach." Please see the Table of Contents here: <https://psycnet.apa.org/journals/hea/39/9>.—KEF

 Karina W. Davidson and  Jazmin N. Mogavero, Center for Personalized Health, Northwell Health, New York, New York; Alexander J. Rothman, Department of Psychology, University of Minnesota.

This study was supported by the National Institutes of Health (NIH) Science of Behavior Change Common Fund Program through an award administered by the National Institute on Aging (U24AG052175). Karina W. Davidson is a member of the United States Preventive Services Task Force (USPSTF). This article does not represent the views and policies of the USPSTF.

Correspondence concerning this article should be addressed to Karina W. Davidson, Center for Personalized Health, Northwell Health, 130 East 59th Street, Suite 14C, New York, NY 10022. E-mail: kdavidson2@northwell.edu

structs, and to identify strategies that can be used to engage those constructs. Taken together, early phase studies can enable investigators to conduct mechanistic trials that test key assumptions regarding the mechanism of action that underlies a proposed intervention.

Yet, despite their evidentiary value, the availability of funding to support the design and conduct of early phase studies is limited. As a result, many investigators select to address only one or a subset of questions regarding an intervention's mechanism of action while leaving those that remain unanswered. Moreover, the lessons and insights that do emerge from the early phase of a research program are difficult to evaluate. Early phase mechanistic studies are not usually registered at the protocol stage, their results are frequently not published, and their data are not deposited in an open and transparent way. Consequently, it can be difficult to discern the quality of the foundation on which a proposed behavioral intervention rests. This limits our ability to (a) minimize the impact of early phase mechanistic studies that are poorly conceptualized, designed, and conducted and (b) maximize the impact of those that are well conceptualized, designed, and conducted and that support the research program they intend to advance. An evidence base that accounts for our collective successes and failures is essential; thus, we need intervention study protocol publications. These types of publications provide investigators with a structured opportunity to delineate the questions that are addressed in their early phase studies and offer a roadmap for the next steps in intervention development.

To highlight the important role that early phase intervention studies play in the development of behavioral interventions, the Science of Behavior Change (SOBC), funded by the National Institutes of Health, launched an initiative focused exclusively on funding early phase mechanistic studies for health behavior change research programs. This initiative was designed to not only emphasize the importance of conducting studies prior to proceeding with a test of the efficacy of a behavioral intervention in a randomized controlled trial, but also to prompt investigators to engage with the theoretical and methodological challenges that underlie rigorous early phase research. In particular, this initiative prioritized the investigation of the mechanisms of action that are hypothesized to underlie a health behavior intervention's effectiveness. To date, even when an initial intervention study returns some signal of behavior change efficacy, it is unknown if the mechanism of action was engaged as hypothesized and, in turn, was causally responsible for the resulting behavior change. Without this crucial scientific insight, small changes in the behavior change intervention across intervention development studies may cause the intervention to stop working without information about why. Moreover, even in the absence of these modifications, investigators may find that they are working with a set of intervention strategies that insufficiently—and perhaps inefficiently—engage the mechanism of action. To address this issue, the SOBC consortium requested that studies use the experimental method or add to an ongoing study that utilizes this approach and focus on generating evidence that links the proposed behavior change intervention to measured changes in the hypothesized mechanism of action.

What is the experimental method? As applied to health behavior change research, it involves mapping and testing the causal chain that delineates the manner in which a proposed intervention obtains a targeted outcome (Nielsen et al., 2018; Sheeran, Klein, &

Rothman, 2017). To implement this approach, investigators specify the mechanism of action an intervention is hypothesized to engage; identify validated measures of that mechanism of action; test mechanism engagement by experimentally manipulating the intervention; and assess the degree to which the hypothesized mechanism was engaged and, in turn, the degree to which it affected change in the targeted behavior (see Figure 1). In most cases, investigators will need to formulate a program of research comprised of a series of studies that engage with the underlying chain of logic. Early phase studies of each of these links is vital for generating the evidence base that underlies the development of a mechanism-engaging intervention and that, in turn, increases the prior probability that a rigorous test of the full intervention will indicate it is effective.

Because advancing behavior change intervention development requires a rigorous evidence base that is transparent, open, and easily accessible, the SOBC consortium also required investigators to specify how they would engage with prevailing open science practices in the design and conduct of these studies. The prevalence of publication bias (also referred to as the “file drawer problem”) in protocols and findings results in significant limits on the lessons that can be learned from these early phase mechanistic studies.

This special issue is designed to illustrate how 10 investigative teams, working across a diverse array of behavioral domains, are pursuing early phase work to generate an evidence base that will advance the development of behavior change interventions. In addition, the papers describe how different types of designs, protocols, and data types can be registered, deposited, and made available to ensure rigor and reproducibility. Two commentaries (Hekler & King, 2020; West, 2020) reflect on the processes used to conduct and communicate early phase research and delineate how efforts to optimize the impact of this work depends on the infrastructure and resources available to investigative teams.

Organized by the main objective (i.e., prevention or treatment) of the behavior change intervention being investigated, we provide a brief overview of each of these 10 initiatives.

Prevention

Birk and colleagues test fear of recurrence as a mechanism of action to improve medication adherence behavior in patients with an

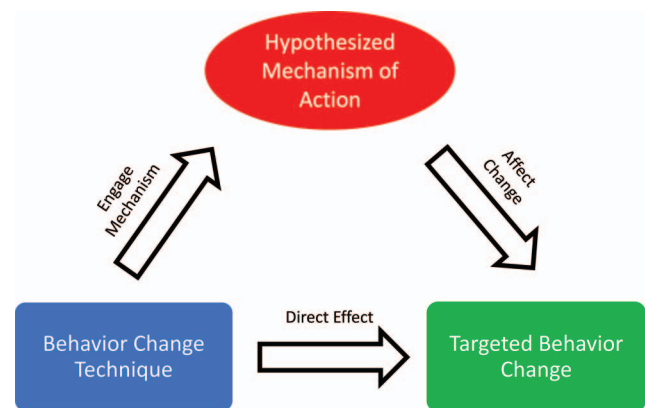


Figure 1. The experimental method as applied to health behavior change research.

acute coronary syndrome and who present to the Emergency Department (Birk et al., 2020). By embedding this test within a double-blind, parallel-group randomized clinical trial, researchers can determine if electronic tablet-delivered, cognitive-bias-modification training intervention compared to a sham control improves fear of recurrence and consequently improves medication adherence. The authors preregistered their trial protocol at ClinicalTrials.gov (NCT03853213) and on the Open Science Framework (OSF; <https://osf.io/k7g8c/>). All planned and exploratory analyses, protocol updates, and measures and the consent form can be found on their OSF page.

In the Halbert report, the rationale, design, and methods for a different type of early phase study protocol are described (Halbert et al., 2020). Given the failure to attain reach, recruitment, retention, and successful behavior change in African American women cancer survivors, the authors determined that acceptability, relevance, and appropriate choice of behavior and mechanism targets needed to be established first. This protocol describes the need to (a) characterize the type of stress reactivity among African American breast cancer survivors based on socioeconomic (e.g., financial toxicity), clinical, and social stressors experienced, (b) examine the impact of stress reactivity on temporal discounting (the hypothesized mechanism of action), and (c) determine the extent to which stress reactivity is associated with adherence to recommendations for cancer control behaviors and treatment. Among other activities, the authors will perform a laboratory-based study with the Trier Social Stress Test as the validated measure of stress reactivity to assess its effect on temporal discounting and cancer control behaviors. Their initial steps then will lead to the design of a stress or behavior change intervention that can target relevant stressors and behavior change outcomes for this important group of underserved and understudied patients. They have registered their study at ClinicalTrials.gov (NCT03881085) and will deposit data both there and on OSF once statistical analyses have been completed.

Mackiewicz Seghete and colleagues report on a protocol for a mechanistic study of Mindfulness Based Cognitive Therapy (MBCT) during pregnancy to ultimately prevent depression (Mackiewicz Seghete et al., 2020). The hypothesized mechanisms of action include emotion regulation by patient report as well as secondary emotional arousal and reactivity assessed by MRI scans of whole-brain activation when participants (a) regulate emotional responding and (b) engage in cognitive control. This will be a two-arm randomized trial with MBCT compared to usual care to test its ability to engage the hypothesized mechanisms. The authors are providing protocol, statistical analyses, and amendments on ClinicalTrials.gov (NCT03809572) with prior approval of their funding partner, National Center for Complementary and Integrative Health. Given the sensitivity of some information to be obtained from the pregnant participants during behavior change, the authors also obtained a Certificate of Confidentiality from the National Institutes of Health.

Wilson and colleagues report on their protocol to assess the feasibility and effectiveness of the APPEAL intervention, which is designed to promote positive affect as a means to enhance HIV medication adherence (Wilson et al., 2020). Individuals who have reported adherence difficulties will be randomly assigned to the APPEAL program or standard of care and changes in the mechanism of action (i.e., positive affect) will be assessed at follow-up. The study is registered at ClinicalTrials.gov (NCT04035759) and

on OSF. De-identified data and supporting materials, including analytic code, will also be posted on OSF.

Treatment

Brewer and colleagues are examining the role that worry plays in sleep disturbance and insomnia (Brewer, Roy, Deluty, Liu, & Hoge, 2020). They describe the protocol for a mechanistic randomized controlled trial to test whether adding an app-based mindfulness training for anxiety to standard treatment will lead to enhanced changes in nonreactivity and worry and whether these changes, in turn, lead to improvements in sleep quality. The study is registered at ClinicalTrials.gov (NCT03684057) and results and study documents will be reported accordingly. Data and analysis code will be made available to qualified researchers by request.

Dong and colleagues are examining whether enhancing the communication and behavior change strategies parents use with their children can improve adolescent sleep behavior (Dong et al., 2020). Their protocol describes a single-arm or 'open' trial of the Parent Behavior Change Intervention (PBC-I), which is being added to a previously validated behavioral sleep intervention for adolescents. The PBC-I is hypothesized to promote parents' use of positive conversational strategies that, in turn, should lead to reduced parent-adolescent conflict and improved sleep outcomes. The study is registered at ClinicalTrials.gov (NCT03926221) and on OSF (<https://osf.io/npm5g/>). De-identified data and supporting materials including analytic code will be posted on OSF and GitHub.

Leahey and colleagues report on a mechanistic randomized controlled trial to test whether training people to engage in episodic future thinking (EFT) will increase the tendency to engage in delayed discounting (DD) and, in turn, promote physical activity and weight-loss maintenance (Leahey et al., 2020). Participants who lose at least 5% of their initial body weight during a weight-loss program will be randomized to a weight-loss-maintenance (WLM) program that either does or does not include EFT training. Measures of the mechanism of action (DD) will be assessed at multiple points during the WLM program. The study is registered at ClinicalTrials.gov (NCT03824769) and results will be reported accordingly, but limits will be placed on the availability of data and analysis code.

McHugh and colleagues report on their protocol to assess the effectiveness of two intervention strategies—cognitive reappraisal and affect labeling—to reduce stress reactivity in response to a standardized stressor among adults who are diagnosed with opioid-use disorder and, in turn, determine whether the reduction in reactivity leads to better distress tolerance (McHugh, Nguyen, Fitzmaurice, & Dillon, 2020). The experimental design affords the opportunity to compare the effect of the two intervention strategies to a psychoeducational control condition, and the underlying mechanism of action will be assessed with both self-report and physiological indicators. The study is registered at ClinicalTrials.gov (NCT03616379), and the principal investigator also maintains a page on OSF (<https://osf.io/8ns7y/>) describing all of the work in her lab. Because of the sensitive nature of the data collected, de-identified data will be made available in accordance with applicable regulations.

Otto and colleagues present a mechanistic randomized controlled trial protocol for engaging distress tolerance and working

memory (two putative mechanisms of action) to improve smoking relapse rates in smokers from lower socioeconomic living circumstances (Otto et al., 2020). They test if the proposed mechanisms of action are improved during stressful nicotine-deprivation windows—when the mechanism would or would not aid in smoking cessation maintenance. They also combine mindfulness with interoceptive exposure as their behavior change intervention to better target their putative mechanisms of action. ClinicalTrials.gov (NCT03565497) and OSF registries were selected for data and measure deposit.

Scioli and colleagues report on a mechanistic randomized controlled trial that compares an exercise intervention to a wait-list symptom-monitoring condition with veterans with chronic low back pain and posttraumatic stress disorder (PTSD) (Scioli et al., 2020). This study aims to demonstrate the feasibility of procedures and elucidate mechanisms relevant to developing individually prescribed, motivationally based exercise regimens to reduce chronic pain, depression, and PTSD symptoms. By using the SOBC experimental medicine approach to investigate hypothesized relationships between exercise-training, neuropeptide Y system function, and neurocognitive testing of reward sensitivity and self-regulation, they will explore if mechanistic improvements result from increased exercise that, in turn, leads to better exercise maintenance and improved psychological function. The study is preregistered at ClinicalTrials.gov (NCT03644927) and on OSF (<https://osf.io/epfmk/>). Final data sets underlying all publications and conference presentations resulting from this research will be shared in electronic format on OSF through a de-identified, anonymized dataset.

Discussion

The 10 protocol papers provide us with a window into the planning and preparatory work that these investigative teams are undertaking as they pursue answers to questions that can guide the implementation and testing of their behavioral intervention. In each case, the investigators have identified a mechanism or set of mechanisms of action that are hypothesized to underlie the intervention's effect on the targeted behavioral outcome. Furthermore, evidence that the intervention can experimentally manipulate the mechanism(s) and, secondarily, that changes in the mechanism(s) are associated with changes in the outcome are considered the primary criteria for moving forward with the proposed program of research. Although the protocols in these papers are well aligned with the framework set out by the SOBC, the opportunity to review them collectively revealed a number of issues that investigators must continue to grapple with as they design and conduct studies that advance intervention development.

First, early phase mechanistic studies such as the ones in this issue are designed to generate evidence that the proposed interventions lead to changes in specified mechanisms but little is said about the magnitude of change that needs to be observed. We recognize that identifying these criteria is challenging—especially when the theoretical models that underlie much of this work provide limited guidance—but explicitly specifying the behavioral outcomes associated with different magnitudes of change in the targeted mechanism will allow investigators to make informed decisions about whether to proceed from a successful mechanistic trial to a full test of the intervention. Moreover, the process of

setting these criteria will encourage investigators to think through the parameters that are most important. For example, should they prioritize the magnitude of change observed or the durability of the observed change over a period of time?

Second, investigators may want to articulate what research strategies they will consider if the early phase study fails to provide evidence to support proceeding to an efficacy trial. Approaches such as the Multiphase Optimization Strategy (MOST; Collins, 2018) may prove useful as it can assist investigators with experimentally specifying the essential components within an intervention. Moreover, it may encourage investigators to pursue competitive tests of strategies designed to engage the hypothesized mechanism of action. This may prove particularly valuable in domains where eliciting sufficient change in the mechanism can be challenging.

Third, engagement with open science practices through each phase of the research life cycle will ensure that the broader research community can benefit from all of the evidence that emerges from our research efforts. Moreover, the process of preregistering early phase mechanistic studies provides a structured framework through which to consider this evidence.

Given that, more often than not, studies in the early phase of a research program are not funded, published, praised, or monitored for transparency and availability, the fact that investigators incorporate them into their behavior change intervention research programs is somewhat surprising. This special issue is dedicated to disseminating new approaches to early phase intervention development. The field of behavior change will be transformed by the process of publishing the design and protocol prior to conduct, incorporating the testing of validated measures of mechanisms of action, committing to open science practices, and communicating how such early phase studies progress. These articles collectively show the way forward.

References

- Birk, J. L., Cumella, R., Lopez-Veneros, D., Jurado, A., Romero, E. K., Lazarov, A., & Kronish, I. M. (2020). Intervening on fear after acute cardiac events: Rationale and design of the INFORM randomized clinical trial. *Health Psychology, 39*, 736–744. <http://dx.doi.org/10.1037/hea0000853>
- Brewer, J. A., Roy, A., Deluty, A., Liu, T., & Hoge, E. A. (2020). Can mindfulness mechanistically target worry to improve sleep disturbances? Theory and study protocol for app-based anxiety program. *Health Psychology, 39*, 776–784. <http://dx.doi.org/10.1037/hea0000874>
- Collins, L. (2018). *Optimization of behavioral, biobehavioral, and biomedical interventions: The Multiphase Optimization Strategy (MOST)*. Philadelphia, PA: Springer.
- Czajkowski, S. M., Powell, L. H., Adler, N., Naar-King, S., Reynolds, K. D., Hunter, C. M., . . . Charlson, M. E. (2015). From ideas to efficacy: The ORBIT model for developing behavioral treatments for chronic diseases. *Health Psychology, 34*, 971–982. <http://dx.doi.org/10.1037/hea0000161>
- Dong, L., Fine, E. R., Michie, S., Zhou, Q., Mullin, A. C., Alvarado-Martinez, C. G., . . . Tran, M. (2020). Open trial of the Parent Behavior Change Intervention (PBC-I): Study protocol. *Health Psychology, 39*, 785–795. <http://dx.doi.org/10.1037/hea0000873>
- Eldridge, S. M., Lancaster, G. A., Campbell, M. J., Thabane, L., Hopewell, S., Coleman, C. L., & Bond, C. M. (2016). Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development

- of a Conceptual Framework. *PLoS ONE*, *11*(3), e0150205. <http://dx.doi.org/10.1371/journal.pone.0150205>
- Freedland, K. E. (2019). The Behavioral Medicine Research Council: Its origins, mission, and methods. *Health Psychology*, *38*, 277–289. <http://dx.doi.org/10.1037/hea0000731>
- Freedland, K. E. (2020). Pilot trials in health-related behavioral intervention research: Problems, solutions, and recommendations. *Health Psychology*. Advance online publication. <http://dx.doi.org/10.1037/hea0000946>
- Halbert, C. H., Jefferson, M. S., Danielson, C., Froeliger, B., Giordano, A., & Thaxton, J. E. (2020). An observational study and randomized trial of stress reactivity in cancer disparities. *Health Psychology*, *39*, 745–757. <http://dx.doi.org/10.1037/hea0000882>
- Hekler, E., & King, A. C. (2020). Toward an open mechanistic science of behavior change. *Health Psychology*, *39*, 841–845. <http://dx.doi.org/10.1037/hea0000924>
- Leahey, T. M., Gorin, A. A., Wyckoff, E., Denmat, Z., O'Connor, K., Field, C., . . . Gilder, C. (2020). Episodic future thinking, delay discounting, and exercise during weight loss maintenance: The PACE trial. *Health Psychology*, *39*, 796–805. <http://dx.doi.org/10.1037/hea0000860>
- Mackiewicz Seghete, K. L., Graham, A. M., Lapidus, J. A., Jackson, E. L. A., Doyle, O. J., Feryn, A. B., . . . Dimidjian, S. (2020). Protocol for a mechanistic study of mindfulness based cognitive therapy during pregnancy. *Health Psychology*, *39*, 758–766. <http://dx.doi.org/10.1037/hea0000870>
- McHugh, R. K., Nguyen, M. D., Fitzmaurice, G. M., & Dillon, D. G. (2020). Behavioral strategies to reduce stress reactivity in opioid use disorder: Study design. *Health Psychology*, *39*, 806–814. <http://dx.doi.org/10.1037/hea0000862>
- Nielsen, L., Riddle, M., King, J. W., Aklin, W. M., Chen, W., Clark, D., . . . the NIH Science of Behavior Change Implementation Team. (2018). The NIH Science of Behavior Change Program: Transforming the science through a focus on mechanisms of change. *Behaviour Research and Therapy*, *101*, 3–11. <http://dx.doi.org/10.1016/j.brat.2017.07.002>
- Otto, M. W., Zvolensky, M. J., Rosenfield, D., Hoyt, D. L., Witkiewitz, K., McKee, S. A., . . . Smits, J. A. J. (2020). A randomized controlled trial protocol for engaging distress tolerance and working memory to aid smoking cessation in low socioeconomic status (SES) adults. *Health Psychology*, *39*, 815–825. <http://dx.doi.org/10.1037/hea0000858>
- Scioli, E. R., Smith, B. N., Whitworth, J. W., Spiro, A., Esterman, M., Dutra, S., . . . Rasmussen, A. M. (2020). Moderated mediation for exercise maintenance in pain and posttraumatic stress disorder: A randomized trial. *Health Psychology*, *39*, 826–840. <http://dx.doi.org/10.1037/hea0000876>
- Sheeran, P., Klein, W. M., & Rothman, A. J. (2017). Health behavior change: Moving from observation to intervention. *Annual Review of Psychology*, *68*, 573–600. <http://dx.doi.org/10.1146/annurev-psych-010416-044007>
- West, R. (2020). An online Paper Authoring Tool (PAT) to improve reporting of, and synthesis of evidence from, trials in behavioral sciences. *Health Psychology*, *39*, 846–850. <http://dx.doi.org/10.1037/hea0000927>
- Wilson, T. E., Massiah, C., Radigan, R., DeHovitz, J., Govindarajulu, U. S., Holman, S., . . . Taylor, T. (2020). The Positive Affect, Promoting Positive Engagement, and Adherence for Life (APPEAL) feasibility trial: Design and rationale. *Health Psychology*, *39*, 767–775. <http://dx.doi.org/10.1037/hea0000880>

Received April 10, 2020

Revision received May 11, 2020

Accepted May 12, 2020 ■