CGU Faculty Publications and Research   CGU Faculty Scholarship

2015

From Ideas to Efficacy: The ORBIT Model for Developing Behavioral Treatments for Chronic Diseases

Susan M. Czajkowski
National Cancer Institute

Lynda H. Powell
Rush University Medical Center

Nancy Adler
University of California, San Francisco

Sylvie Naar-King
Wayne State University

Kim D. Reynolds
Claremont Graduate University

See next page for additional authors

Follow this and additional works at: https://scholarship.claremont.edu/cgu_fac_pub

Part of the Analytical, Diagnostic and Therapeutic Techniques and Equipment Commons, Diseases Commons, Medical Education Commons, and the Mental and Social Health Commons

Recommended Citation

Authors

Susan M. Czajkowski, Lynda H. Powell, Nancy Adler, Sylvie Naar-King, Kim D. Reynolds, Christine M. Hunter, Barbara Laraia, Deborah H. Olster, Frank M. Perna, Janey C. Peterson, Elissa Epel, Josephine E. Boyington, and Mary Charlson

From Ideas to Efficacy: The ORBIT Model for Developing Behavioral Treatments for Chronic Diseases

13 authors, including:

Susan M Czajkowski
National Cancer Institute (USA)
91 PUBLICATIONS   9,992 CITATIONS

SEE PROFILE

Lynda Powell
Rush University Medical Center
217 PUBLICATIONS   15,044 CITATIONS

SEE PROFILE

Nancy Adler
University of California, San Francisco
447 PUBLICATIONS   41,622 CITATIONS

SEE PROFILE

Barbara Laraia
University of California, Berkeley
155 PUBLICATIONS   9,164 CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:

Project National Growth and Health Study View project

Project SEED: Stress, Eating, and Early Development View project

From Ideas to Efficacy: The ORBIT Model for Developing Behavioral Treatments for Chronic Diseases

Susan M. Czajkowski*
National Heart, Lung, and Blood Institute,
National Institutes of Health, Bethesda, Maryland

Lynda H. Powell*
Rush University Medical Center, Chicago, Illinois

Nancy Adler
University of California, San Francisco

Sylvie Naar-King
Wayne State University

Kim D. Reynolds
Claremont Graduate University

Christine M. Hunter
National Institute of Diabetes and Digestive and Kidney
Diseases, National Institutes of Health, Bethesda, Maryland

Barbara Laraia
University of California, Berkeley

Deborah H. Olster
Office of Behavioral and Social Sciences Research, National
Institutes of Health, Bethesda, Maryland

Frank M. Perna
National Cancer Institute, National Institutes of Health,
Bethesda, Maryland

Janey C. Peterson
Weill Cornell Medical College

Elissa Epel
University of California, San Francisco

Josephine E. Boyington
National Heart, Lung, and Blood Institute, National
Institutes of Health, Bethesda, Maryland

Mary E. Charlson
Weill Cornell Medical College

for the Obesity Related Behavioral
Intervention Trials (ORBIT) Consortium[1]

[1] See Appendix (in online supplemental materials) for a list of ORBIT Project Personnel.

Objective: Given the critical role of behavior in preventing and treating chronic diseases, it is important to accelerate the development of behavioral treatments that can improve chronic disease prevention and outcomes. Findings from basic behavioral and social sciences research hold great promise for addressing behaviorally based clinical health problems, yet there is currently no established pathway for translating fundamental behavioral science discoveries into health-related treatments ready for *Phase III* efficacy testing. This article provides a systematic framework for developing behavioral treatments for preventing and treating chronic diseases. *Method:* The Obesity-Related Behavioral Intervention Trials (ORBIT) model for behavioral treatment development features a flexible and progressive process, prespecified clinically significant milestones for forward movement, and return to earlier stages for refinement and optimization. *Results:* This article presents the background and rationale for the ORBIT model, a summary of key questions for each phase, a selection of study designs and methodologies well-suited to answering these questions, and prespecified milestones for forward or backward movement across phases. *Conclusions:* The ORBIT model provides a progressive, clinically relevant approach to increasing the number of evidence-based behavioral treatments available to prevent and treat chronic diseases.

Keywords: health behavior, behavioral treatment development, translation of basic behavioral research into behavioral treatments, behavioral study designs and methods, prevention and management of chronic disease, lifestyle

Supplemental materials: http://dx.doi.org/10.1037/hea0000161.supp

It is widely acknowledged that behavior plays a central role in the prevention and management of chronic disease. An estimated 40% of premature deaths are attributable to preventable behavioral factors such as smoking, unhealthy dietary intake, and sedentary lifestyle (Mokdad, Marks, Stroup, & Gerberding, 2004; Schroeder, 2007), all of which have been linked to major chronic illnesses such as cardiovascular disease, cancer, and diabetes (Chakravarty et al., 2012; Yoon, Bastian, Anderson, Collins, Jaffe, & CDC, 2014). Unhealthy lifestyles adversely affect health and well-being and increase the cost of health care, an increasingly important consideration given the aging of the U.S. population. Chronic diseases currently account for 85% of health care spending (Anderson, 2010), and the number of Americans who have at least one chronic disease is expected to rise from 145 million in 2009 to 157 million by 2020 (Anderson, 2010).

Engaging in health-promoting behaviors can reduce or delay the onset of chronic disease and disability (Akesson, Larsson, Discacciati, & Wolk, 2014; Mozaffarian, 2014; Paganini-Hill, Kawas, & Corrada, 2011). Treatments that encourage healthy lifestyle behaviors, grounded in fundamental behavioral research and developed incrementally over time, have proven highly effective in reducing such clinically important outcomes as weight, blood pressure, cholesterol levels, and incidence of diabetes (Appel et al., 2003; Appel et al., 2011; Epstein, Paluch, Roemmich, & Beecher, 2007; Knowler et al., 2002; Wadden et al., 2011). Given the potential for evidence-based behavioral treatments to address many of the costly health problems facing an aging population, accelerating their development and optimization is a public health priority.

Translation I research in which "bench" findings are applied to the "bedside" is uncommon in the behavioral arena. Advances in understanding fundamental human processes such as motivation, emotion, cognition, self-regulation, decision-making, stress, and social networks are not being optimally applied to pressing behavioral health problems. Promising behavioral treatments "in the pipeline" are often abandoned, rather than refined, if they fail early tests. In some cases, treatments that achieve success in early studies are not pushed toward rigorous testing in *Phase III* efficacy trials, while others are tested in *Phase III* trials prematurely,

without undergoing adequate development and refinement in early phase studies. This contrasts with the biomedical arena which benefits from industry support for early translational research and has a well-defined process for developing a new drug or device, starting with basic science research and progressing to the FDA-required *Phase III* efficacy trial.

In light of the importance of behavioral treatment development, the National Institutes of Health Office of Behavioral and Social Sciences Research (OBSSR), in collaboration with the National Heart, Lung, and Blood Institute (NHLBI), the National Cancer Institute (NCI), the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and investigators from the Obesity-Related Behavioral Intervention Trials (ORBIT) consortium organized a cross-disciplinary conference of experts in fields related to the development and early testing of behavioral health-related treatments. An important goal of this conference was to propose guidelines for developing behavioral treatments to prevent or manage chronic diseases, proceeding from the identification of innovative approaches to solving important clinical problems based on basic behavioral science theory and research, to the design and preliminary testing of promising treatments, through readiness to conduct a *Phase III* efficacy trial. Conference participants included members of the ORBIT consortium, all of whom are currently developing obesity treatments, NIH program officers, and experts in the discoveries, designs, methodologies, and infrastructures needed to develop and test innovative, health-related behavioral treatments (conference information can be found at http://www.nihorbit.org/ORBIT%20Content/Workshops%20and%20Conferences.aspx?PageView=Shared).

This article presents the ORBIT model for developing behavioral treatments to prevent and/or manage chronic disease. The model was informed by the process of drug development and by previous efforts to define the behavioral treatment development process. It reflects a comprehensive synthesis of the recommendations made by workshop participants as further refined by NIH collaborators and ORBIT consortium members.

The Process of Drug Development

The development of a new drug is guided by regulatory requirements and typically sponsored by industry (Friedman, Furberg, & DeMets, 1998; Lipsky & Sharp, 2001). It begins with preclinical basic science studies in animal or in vitro models to understand the disease process. *Phase I* and *II* studies turn to humans and focus on small numbers of highly selected subjects. *Phase I* "dose-finding" studies determine the maximally tolerated dose of a candidate drug, and *Phase II* studies determine the impact of this maximally tolerated dose on significant biologic activity. If the drug has minimal biologic impact, it is reexamined in *Phase I* and/or preclinical studies or abandoned. If the drug has the expected impact, a pilot study is often conducted to determine the feasibility and acceptability of a trial protocol in preparation for the *Phase III* efficacy trial, where the drug's impact on clinically meaningful endpoints such as disease onset, progression and mortality is evaluated (Friedman et al., 1998; Lipsky & Sharp, 2001). Demonstration of benefit of the drug on clinically significant outcomes in *Phase III* efficacy trials is key to Food and Drug Administration (FDA) approval and introduction of the drug into the commercial market.

Previous Efforts to Define a Process for Behavioral Treatment Development

Because the development of behavioral treatments that target physical health outcomes has not been regulated by any governmental agency, it has not been guided by any widely recognized and agreed-upon process. A number of prior efforts describing behavioral treatment development include: Green's (1974) PRECEDE/PROCEED model for health program planning; Greenwald and Cullen's (1985) 5-phase cancer control model; Flay's (1986) 8-stage health promotion model; the National Institute of Drug Abuse's (NIDA) Stage Model (Carroll & Onken, 2005; Rounsaville, Carroll, & Onken, 2001); the EVOLVE mixed-methods model (Peterson et al., 2013); the Medical Research Council's framework for complex interventions (Craig et al., 2008a, 2008b); and Intervention Mapping (Bartholomew, Parcel, Kok, Gottlieb, & Fernandez, 2011).

The ORBIT model, first introduced in several recent NIH initiatives (National Heart, Lung, & Blood Institute, 2008; Office of

Behavioral & Social Sciences Research, 2010), differs from many of these earlier approaches in several ways. First, it focuses exclusively on the *early, pre-efficacy phases* of behavioral treatment development. This makes it possible to integrate the ORBIT framework with those frameworks that outline steps beyond the pre-efficacy phase (e.g., NIDA's Stage Model, the MRC model, or Intervention Mapping). Second, it was developed for use with a *broad array of chronic diseases,* unlike some of the earlier models which were developed for specific disorders such as cancer, drug abuse, or mental illness. Third, it intentionally *uses terminology from the drug development model* to enhance comprehension by medical gatekeepers who most commonly manage chronic diseases with drug therapy.

The ORBIT Model For Behavioral Treatment Development

Overview

Figure 1 presents the ORBIT model. Critical features include a flexible and iterative progressive process, prespecified clinically significant milestones for forward movement, and return to an earlier phase for refinement in the event of suboptimal results. Although its primary focus is on pre-efficacy development and testing, later phases of research are included to show that optimization of treatments can occur even for those that have reached the efficacy or effectiveness stage. Table 1 presents a summary of key questions of relevance for each phase, a selection of designs and methodologies that are well-suited to answering these questions, and prespecified milestones for forward or backward movement across phases.

Identification of a Significant Clinical Question

Coller (2008) has observed that one of the key skills necessary for a successful translational effort is the ability to articulate a health need or clinical question requiring a solution "with the precision of a basic science hypothesis." Thus, the process of behavioral treatment development is informed by the identification of a clinical question or problem for which a behavioral treatment could provide a solution. For example, the clinical problem could
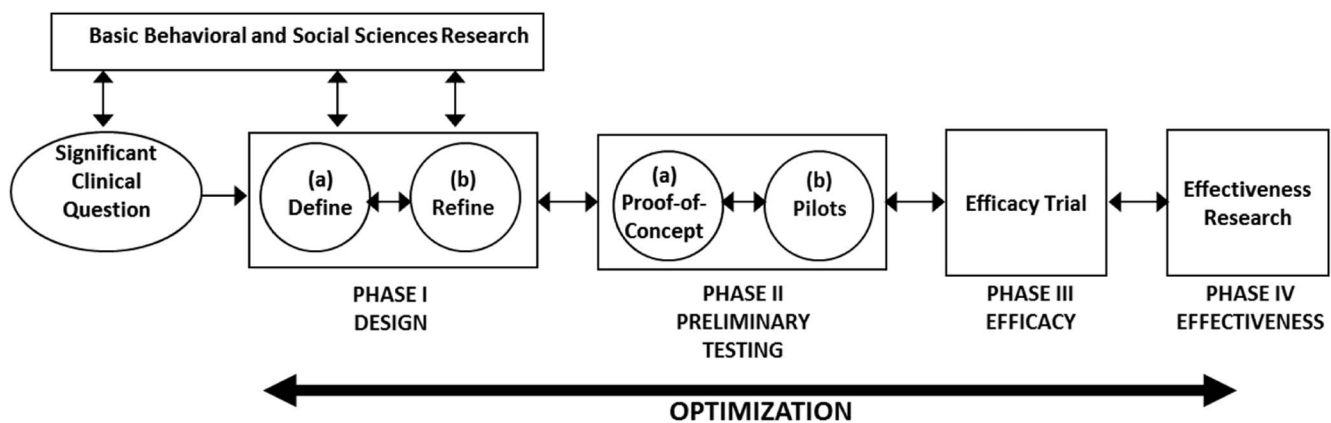
Figure 1. The ORBIT model for behavioral treatment development.

Table 1
Goals, Methods, Spirit of Inquiry, and Milestones, by Phase, in the ORBIT Model

Phase	Central goal	Specific goals	Common methods	Spirit of inquiry	Milestone
Phase Ia: Define	Define basic elements	Develop hypothesized pathway by which behavioral treatment can solve an important clinical problem; Provide scientific basis for behavioral milestones; Provide basic behavioral/social science basis for treatment components and their respective treatment targets; Identify appropriate subjects; Assess safety, tolerability, acceptability	Review of clinical guidelines, meta-analyses, clinical trials, basic behavioral/social science findings, epidemiologic studies; Experiments; Time Series; ABA designs; N-of-1 trials; Ecological observational studies; Formative qualitative research: —focus groups —interviews; Evidentiary studies	Creativity; Discovery; Flexibility; Experimentation; Hypothesis formulation	Candidate treatment components, methods, and milestones are defined
Phase Ib: Refine	Refine for strength and efficiency	Identify independent and interactive treatment components; Determine needed dose/duration; Determine mode of delivery; Determine need for tailoring for: —special populations —treatment response; If needed, optimize treatment using basic behavioral/social science findings; Assess safety, tolerability, acceptability	Factorial/fractional factorial designs; Adaptive designs; Experiments; Time series; Single case designs; Case series; Adaptive treatments; Formative qualitative research: —focus groups —interviews; Signal detection methods	Efficiency; Tailoring; Clinical relevance; Sensitivity to patient; Optimization; Flexibility	Satisfaction that the treatment package is complete and the fixed protocol is ready for testing
Phase IIa: Proof-of-concept	Clinically significant signal	Prepare the Treatment Manual and procedures for fidelity monitoring; Determine whether the treatment can achieve a clinically significant signal on the behavioral risk factor	Quasi-experimental, treatment-only design	Initial test of a fixed protocol	A clinically significant impact on the behavioral target
Phase IIb: Pilot testing	Clinically significant signal over noise	Replication of clinically significant signal in treated group; Clinically significant signal over noise; Adequacy of control group: —minimal change in behavioral risk factor —minimal dropouts and crossovers —credible and acceptable	Randomized designs	Randomized test of a fixed protocol; Systematic study of control group	Empirical support that: —the intervention has a clinically significant signal over the control group —the control group is appropriate

Table 1 (*continued*)

Phase	Central goal	Specific goals	Common methods	Spirit of inquiry	Milestone
Phase IIb (continued): Feasibility pilot	Feasibility of efficacy trial protocol	Prepare the Manual of Operations for efficacy trial protocol Determine logistical feasibility of efficacy trial protocol for investigators and participants Provide estimates needed for design of efficacy trial: —screening to enrollment ratio —dropout/crossover rates —response rates in treated and control conditions	Qualitative and quantitative studies of feasibility & acceptability	Acceptability to target population Performance across multiple sites Preparation for efficacy trial: —sample size —length of follow-up —number of sites	Empirical support that the trial protocol is logistically feasible Empirically derived estimates available for the design of an efficacy trial

be that there is no current treatment for a specific condition, a current treatment is not potent or durable enough to change an important clinical outcome, a current treatment is effective but adherence to it is poor, or a current treatment produces too many side effects for routine use in clinical practice.

The hypothesis that change in a behavioral risk factor could solve a clinical problem is one of the entry points for behavioral treatment development (depicted in Figure 1 by the arrow going from "Significant Clinical Question" to *Phase I* studies). The initial explicit identification of the clinical problem does several things. It encourages investigators to: (a) set sights on the *Phase III* efficacy trial which will test the benefit of the behavioral treatment on an outcome that is meaningful in clinical practice; (b) consider early on the primary behavioral, clinical, or biomedical endpoints in that efficacy trial; and (c) commit to achieving a sufficiently potent level of behavioral change to achieve meaningful change on the ultimate biomedical or clinical outcome.

Application of Basic Behavioral and Social Sciences Research

Basic behavioral and social sciences research can foster hypotheses about the *drivers* of a behavioral risk factor. Treatment development would then proceed with the translation of these drivers of behavior into treatment *targets*, an identification of clinical methods by which these targets can be altered, and the translation of targets into quantifiable process measures to assess the success of the treatment. For example, basic behavioral science has shown that mobilization of executive function can serve as a "brake" on impulsive eating (Fagundo et al., 2012). Thus, it is reasonable to hypothesize that improvement in executive function would reduce impulsive eating. Treatment development would then involve identifying specific executive function skills such as planning and problem-solving, designing a training program to teach these skills, and developing process measures to assess mastery.

The reciprocal connection between basic behavioral and social sciences research and early phases of behavioral treatment development is depicted in Figure 1 by bidirectional arrows. Although a clinical problem can foster a search for relevant basic science guidance, basic science discoveries can inspire an application of that process to a pressing clinical problem. Various independent basic science findings can justify inclusion of several candidate treatment components, each with their own treatment targets, clinical methods, and process measures. Basic science can inform the dose and method of delivery of a behavioral treatment. If a treatment approaches, but does not achieve, clinically significant milestones, avenues for optimization may also be informed by basic science findings.

Phase I: Design

The goal of *Phase I* is to design the essential features of a behavioral treatment or to adapt an existing treatment to a new problem. The hallmark is that the testing is fluid, permitting ongoing adjustments in treatment in response to evolving findings. Although initial tests may be on a small number of highly selected participants, milestones for judging success of the treatment should be ambitious, providing a needed cushion for expected erosion of effect in subsequent testing in more diverse samples.

Phase Ia: Define

Purpose and goals. In *Phase Ia*, the scientific foundation and the basic elements of the behavioral treatment are defined. Among the goals are the development of a hypothesized pathway by which a behavioral treatment could solve a clinical problem, specification of clinically significant milestones on the behavioral risk factor being targeted, identification of appropriate subjects, definition of potential treatment components, and elucidation of basic behavioral and social sciences support for potential treatment components and their respective treatment targets.

Milestones for judging the success of a treatment on the behavioral risk factor are guided by the clinical problem. A priori specification of these milestones prevents "moving the target" after the data are in. Basing milestones on clinical significance avoids the problem of erroneously assuming that a treatment or treatment component is successful if it produces a small benefit that is statistically significant but not clinically meaningful. Milestones can be identified from epidemiological, experimental, or clinical studies which link the behavioral factor to accepted biomedical risk factors, surrogate markers, subclinical disease, or clinical events. Finding a cutpoint on a behavioral measure where biomedical risk increases is suggestive of a level of change in the behavioral factor that is clinically relevant. This may be an easier task for established behavioral risk factors such as smoking, alcohol/drug abuse, diets high in saturated fat or sodium, physical inactivity, stress, depression, and low social support, all of which have an evidence base to support cutpoints for increased risk. However, in the case of novel behavioral risk factors where such an evidence base may not exist, *Phase Ia* experimental studies examining covariation between the behavioral factor and a relevant biomedical risk factor would be justified. For example, weight loss of ≥5% in overweight and obese adults with cardiovascular disease (CVD) risk factors can be deemed a clinically significant change because it has been shown to result in clinically meaningful cardiovascular and metabolic benefits (Jensen et al., 2013). Were these data not available, *Phase Ia* experimental studies examining the covariation between level of weight loss and a cardiovascular risk factor, such as blood pressure, would be needed.

Study designs and methods. A range of designs and methods are appropriate for Phase Ia studies. Systematic reviews, meta-analyses, and epidemiologic studies can be used to identify clinically significant problems, endpoints, milestones, and links between behavioral risk factors and clinical endpoints. Taxonomies and "mapping" strategies that characterize behavioral interventions and their components can help in selecting treatment elements (Michie, van Stralen, & West, 2011; Bartholomew et al., 2011). Experimental and observational studies in the laboratory and field enable the researcher to identify potential treatment components and the respective biological, psychophysiological, social, environmental, and behavioral targets needed to accomplish change in them and, in turn, in the behavioral risk factor. Ethnographic observation and interviews, focus groups, and other qualitative research methods can engage the community of participants in the development of user-centered strategies and help identify attitudes, norms, and values that can affect an intervention's acceptability and feasibililty (Peterson et al., 2013; Strolla, Gans, & Risica, 2006). Observational techniques such as behavioral event modeling (Wansink, 2010) and use of ecological momentary assessment (Shiffman, Stone, & Hufford, 2008) permit the study of behavior in naturalistic settings, leading not only to the identification of intervention targets but also of critical time points for intervention delivery. Time series and ABA designs, involving multiple baseline and treatment observations in small numbers of individuals (Ridenour, Pineo, Molina, & Lich, 2013), allow researchers to identify early indications of potential benefit. New analytic techniques for use with small samples, including Bayesian analyses of data from N-of-1 trials, may be useful (Zucker, Ruthazer, & Schmid, 2010). *Phase Ia* studies are consistent with "evidentiary studies" (Stevens, Taber, Murray, & Ward, 2007), a term used to describe a series of small, inexpensive experiments or observational studies of the impact of potential treatment components on process variables.

Milestones. Movement to *Phase Ib* is warranted once the hypothesized pathway by which the proposed treatment translates into benefit on the behavioral risk factor is formulated, potential candidates for treatment components have been assembled, intervention targets for each component have been delineated, and milestones for determining clinically significant change on the behavioral risk factor have been defined.

Phase Ib: Refine

Purpose and goals. The goal of *Phase Ib* is to refine the treatment to promote efficiency while at the same time retaining sufficient strength to promote clinically significant change. Candidate components are examined together for the first time, and those that are essential and show independent effects on the behavioral risk factor are identified. The impact of serial presentation of independent components might be studied. Practical aspects of the intervention such as mode of delivery, agent of delivery, frequency of contact, and duration of contacts are studied to identify the most efficient ways to achieve clinical targets. In cases of variable response to a single protocol, the development of adaptive treatments with tailoring for special population subgroups or for differential response to treatment could be considered. *Phase Ib* studies are ideally suited to the adaptation of an existing treatment to new conditions, such as a new patient population, setting or context, or mode of delivery.

Study designs and methods. Factorial and fractional factorial designs (Chakraborty, Collins, Strecher, & Murphy, 2009) are ideal for determining independent treatment components or combinations of components, optimum methods of delivery, and optimum doses of treatment. Small single case or case series studies can be used to evaluate dose, safety, tolerability, and impact of introduction of new treatment components (Dallery & Raiff, 2014; Kazdin, 1982). Adaptive designs provide the methodology for determining the impact of serial introduction of multiple treatment components (Lei, Nahum-Shani, Lynch, Oslin, & Murphy, 2012). Modeling techniques derived from engineering and control systems theory can simulate intervention effects within complex systems to determine how to achieve maximum benefit (Navarro-Barrientos, Rivera, & Collins, 2011). Analytic procedures drawn from engineering can quantify the patterns of treatment effects over time to determine the appropriate timing for evaluating its effects on a behavioral risk factor (Navarro-Barrientos, Rivera, & Collins, 2011). An adaptive treatment, rather than a "one size fits

all" treatment, could be developed to feature tailoring based upon prespecified decision rules for participant characteristics or response to treatment (Lei, Nahum-Shani, Lynch, Oslin, & Murphy, 2012). Signal detection methods can be useful for identification of subgroups for which tailoring of treatment could optimize their outcomes (Palmer & Hadley, 2005). Qualitative methods evaluate acceptability to the target population and help refine the content and delivery of the treatment package (Strolla, Gans, & Risica, 2006).

Milestones. The essential milestone for moving to *Phase II* is the confidence of the investigator that the treatment package is complete, includes essential components offered in an efficient way, is safe and acceptable to the population of interest, and promises to have a clinically significant benefit on the behavioral risk factor. Evidence of these achievements signals that the completed treatment protocol is ready to undergo a "proof-of-concept" test.

Phase II: Preliminary Testing

The goal of *Phase II* studies is to test the ability of a fixed treatment package to produce a clinically significant improvement on a behavioral risk factor. The hallmark of *Phase II* studies is that the treatment protocol is fixed and clearly articulated in a treatment manual. Two types of testing can be conducted, often serially. A preliminary, proof-of-concept test is a cost-effective way to determine *if* a treatment package can achieve benefit on a clinically significant target in a small, select sample. If it does, it justifies going forward with more rigorous and costly pilot testing using a randomized design and larger, more representative samples. Sequential testing, beginning with a small proof-of-concept test, avoids wasting the resources needed for a more ambitious randomized design on a treatment that cannot hit clinically significant targets under optimum conditions.

Phase IIa: Proof-of-Concept

Purpose and goals. The main goal of the proof-of-concept study is to determine, in an efficient way, whether or not the treatment merits more rigorous and costly testing using a randomized design. This is done by determining if the treatment package that emerges from *Phase I* studies can produce a clinically significant improvement on the behavioral risk factor under ideal conditions. Because the protocol is fixed, a Treatment Manual can be written that promotes quality assurance, including materials for training, ongoing supervision, and fidelity monitoring of interventionists.

Study designs and methods. Quasi-experimental, within-subjects designs where subjects act as their own controls in a pre-post comparison are ideal. The sample size can be small because clinical, not statistical, benefit is sought and sample size calculations are unnecessary. The sample can be selected from accessible subjects, rather than be representative, because this initial test will determine only whether the treatment merits more rigorous testing. The focus of *Phase IIa* studies is deliberately placed on the treatment and its ability to produce clinically significant change on a behavioral risk factor. This is in contrast to *Phase IIb* concerns with determining the source of a treatment effect (e.g., separation of treatment effects from effects due to the

passage of time) and with choosing the appropriate control group, in itself a complex undertaking (Mohr et al., 2009).

Milestones. The essential milestone for moving to *Phase IIb* is that the treatment achieved a clinically significant change on the behavioral risk factor. If an ambitious clinical criterion was approached, but not achieved, optimization using qualitative inquiry could justify forward movement to *Phase IIb*. If the clinical criterion was not even approached, the researchers could return to *Phase I* studies or decide if there is justification to abandon the treatment.

Phase IIb: Pilot Testing

Purpose and goals. Pilot studies have a variety of purposes and can take many forms, but the proposed model includes two general types: pilot studies and feasibility pilot studies. Pilot studies are natural follow-ups to a positive proof-of-concept study. Their main goal is to determine whether a clinically significant benefit on the behavioral risk factor can be achieved in a larger, more representative sample and whether this benefit is above and beyond the passage of time, nonspecific attention, or other treatment options. There are many choices for a control group, ranging from a less stringent usual care control to a more stringent attention control (Freedland, Mohr, Davidson, & Schwartz, 2011; Kraemer, Mintz, Noda, Tinklenberg, & Yesavage, 2006). At minimum, all controlled designs control for the passage of time by determining whether the subject would have achieved benefit over time without treatment. The specific choice of the type of control should be based upon the clinical question of interest. For example, some questions focus on the treatment and determine whether or not it can do better than nonspecific attention. Other questions focus on the outcome and determine whether or not the new treatment can do better than usual care, or as well as an existing treatment but with less burden and cost (Freedland et al., 2011). Once the decision about the appropriate control is made, systematic study of the control group's properties is needed (Mohr et al., 2009). *Phase IIb* is an ideal time to study the control group's credibility, dropout rate, and influence on the behavioral risk factor.

Feasibility pilot studies serve as preparation for the *Phase III* efficacy trial. Their key purpose is to assess the feasibility of the trial protocol and provide estimates needed to design the efficacy trial. Is the trial protocol feasible and acceptable to the investigators and to the participants? Is there differential drop-out from the randomized arms? What is the screening to enrollment ratios overall and at each of the recruiting sites? Although a feasibility pilot study produces an unstable estimate of the effect size on the primary endpoint of the *Phase III* efficacy trial (Kraemer et al., 2006), the effect size should be assessed and considered along with accumulated effect sizes from similar past trials to determine the sample size needed for the efficacy trial.

Study designs and methods. Most types of pilot studies use a randomized design. Systematic evaluation of a variety of control groups can proceed using fractional factorial designs. Feasibility pilot studies draw on qualitative methods, such as focus groups and ethnographic interviews, to assess participant and staff acceptance of, and preference for, all aspects of the protocol including methods and measures, treatment and control conditions and procedures, and quality assurance protocols. Findings can facilitate

protocol refinement and simplification in light of direct experience.

Milestones. *Phase IIb* data showing that a behavioral treatment produces a clinically significant signal on the behavioral risk factor in patients with the specified clinical problem—although the chosen control does not—supports moving to a *Phase III* efficacy trial. Empirical support for the feasibility of the trial protocol includes a conservative and feasible recruitment plan, an estimate of drop-out rates from both treated and control conditions, and an estimate of the probable range of effect from treated and control conditions that will be attained on the proposed primary clinical endpoint in the efficacy trial.

Application of the ORBIT Model

The ORBIT model proposes a set of studies forming a chain of evidence that signals readiness for an efficacy trial. This chain of evidence can be translated into a pathway by which the treatment is hypothesized to work (see Figure 2). The link between A and B demonstrates that the treatment has fidelity; it can produce change on its intended behavioral, social, or environmental targets. The link between A and C shows that the treatment is powerful enough to produce clinically significant improvement in the behavioral risk factor of interest. A fully powered determination of the causal links between A and D or E would occur in an eventual efficacy trial.

The value of articulating a hypothesized pathway, and collecting measurements for each of its links, lies in the ability to more precisely interpret the results of *Phase III* trials (Powell et al., 2008). If the trial produces positive results, evidence specifically supporting each link of the chain strengthens the assertion that the observed effects were due to *hypothesized* pathways. Evidence collected for each link of the chain in negative trials can help determine whether null findings were due to a *failure of the hypothesis* that change in the behavioral risk factor is causally related to change in the biomedical outcome or a *failure of the treatment* to affect its targets.

Use of the ORBIT model is illustrated by applying it to the development of a technology-assisted behavioral treatment to prevent diabetes in insulin resistant patients, justified by clinical guidelines indicating that lifestyle change is the first step in treatment (Handelsman et al., 2011). The scenario below shows how the model could be implemented to develop and test such an intervention.

Using the ORBIT model, a *Phase Ia* review of epidemiological studies and clinical trials provides empirical support for the clinical significance of a 30% reduction in diabetes over standard drug treatment (Hamman et al., 2006), a 5% weight loss as a biomedical target (Hamman et al., 2006), a dietary change of 5% reduction in percent fat, and an increase in physical activity to 150 min/week of moderately vigorous physical activity (Hamman et al., 2006).

Phase Ia investigation of basic science studies shows both theoretical and empirical support for the value of daily self-monitoring on reducing fat in the diet and increasing physical activity.

A *Phase Ia* test of daily self-monitoring in a small *N* time series of selected patients shows that patients will self-monitor both their dietary intake and their physical activity, as evidenced by their willingness to transmit data from daily food diaries and accelerometers. Although the goals of a 5% reduction in fat and physical activity target of 150 min/week are achieved, they are not sustained over time. Based on further review of basic science studies suggesting that tailored feedback potentiates the effects of self-monitoring, Internet-delivered tailored feedback is added to the *Phase Ia* small *N* time series study and receipt of the feedback is measured by frequency of patient log-ins. With this addition, sustained achievement of the diet and physical activity milestones is obtained.

A subsequent *Phase Ib* fractional factorial study determines that daily self-monitoring and tailored feedback together are more potent than is either one alone in achieving the 5% weight loss (biomedical) target. The combined findings suggest that a treatment with two components is needed and the effects are robust enough to move to *Phase II* studies, at which point a Treatment Manual would be written and a treatment-only "proof-of-concept" study is run on a small number of accessible patients. If the dietary, physical activity and weight loss milestones are achieved, this justifies a more robust pilot test in a larger, more diverse sample of patients using a randomized design. Such a series of studies make it possible to articulate the hypothesized pathway by which the proposed treatment may improve the biomedical or clinical outcome (see Figure 3).

All of the studies presented in this illustration could be conducted by a single investigator, by a single team of investigators, or by a group of investigators who are, at best, loosely connected. An assumption of the ORBIT model is that research efficiency and quality are enhanced when a multi-disciplinary collaborative team of investigators works to integrate diverse studies into a chain of evidence that justifies a *Phase III* efficacy trial.

Summary and Conclusions

Given the vital role of behavior change in delaying or mitigating the effects of costly chronic diseases, effective and durable behavioral treatments are urgently needed. The ORBIT model was developed to identify the most productive ways to accomplish this. It provides guidance on the *process* of treatment development, but does not propose any specific *content*. It suggests that use of a progressive, transdisciplinary framework to facilitate the translation of basic behavioral science findings to clinical application will strengthen behavioral treatments, encourage their testing in rigorous efficacy and effectiveness trials, enhance success, and foster dissemination into clinical practice.

Figure 2.   Model of pathway by which a behavioral treatment is hypothesized to improve a clinical outcome (CSΔ = clinically significant change). See the online article for the color version of this figure.
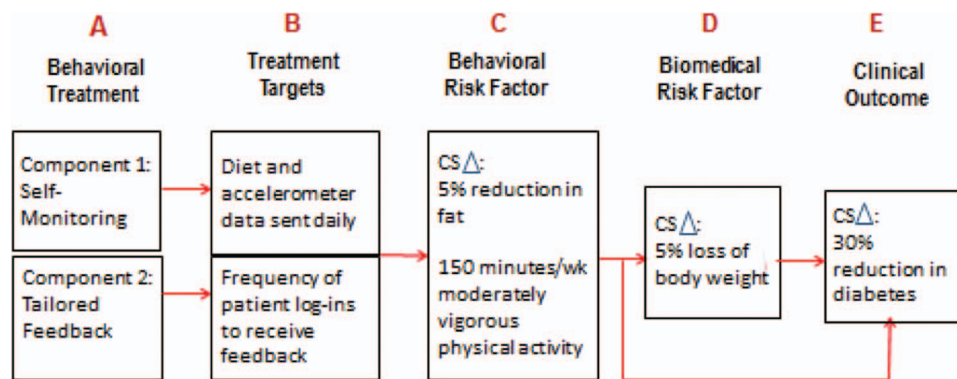
Figure 3. Illustration of a pathway by which a weight loss treatment is hypothesized to reduce diabetes (CSΔ = clinically significant change). See the online article for the color version of this figure.

Currently, all of the elements needed to go from ideas to the efficacy trial exist, but the pathway for doing so is not well-defined. Without the early discovery and innovation that is characteristic of basic science, the potential for behavioral treatments to be robust enough to produce clinically significant results is undercut. Without a progressive approach to treatment development that embraces a variety of designs and methods, there is a risk that promising treatments will be abandoned prematurely because they fail tests that are too stringent for an evolving understanding of their fundamental elements. Without input from clinical practice, treatments that are judged to be successful because they achieve statistical significance may produce results that are too small to be clinically meaningful. Without a consistent framework to encourage progression toward the behavioral efficacy trial, the ability of behavioral and social science researchers to provide the type of evidence that is meaningful to clinical gatekeepers and third-party payers is compromised.

The ORBIT model stitches together these existing crucial elements in the behavioral sciences in several ways. First, it pushes behavioral and clinical investigators to set sights on the efficacy trial, identifies the chain of evidence needed to support such a trial, and outlines the careful, progressive program of research that can provide this evidence.

Second, the ORBIT model encourages a transdisciplinary approach. Crosstalk between basic and applied behavioral and social scientists can foster innovative approaches to common problems, such as novel methods for motivating patients to stick with early changes, sustaining change by mobilizing social networks, or maximizing executive function as a way to minimize impulsivity. Crosstalk between clinicians in medical practice and applied behavioral scientists can increase the significance of the questions posed and identify targets that have meaning in clinical practice. Such crosstalk can facilitate the evaluation of a behavioral treatment's viability as an alternative or adjunctive treatment, its side-effect profile, its effects on quality of life, and its potential cost-effectiveness relative to existing treatments.

Third, the ORBIT model advocates for flexibility in both the designs and methodologies used for treatment development. In the early phases, it encourages investigators to draw on clinical acumen and creativity to "tweak" treatments in response to ongoing results as treatments unfold. This type of work can and should be clearly separated from the testing of fixed protocols. Currently, most behavioral treatments are tested in the same way using randomized designs with attention control groups, fixed protocols, and blinding to outcomes until follow-up is complete. There is a strong rationale for such methods, but when used universally, particularly in the early phases of treatment development, their use can undercut creativity, impede discovery, and produce weak treatments.

Fourth, the ORBIT model provides a language for conveying the significance of a small, single study. Small, early phase studies run the risk of being judged to be not very important. However, if they are conceptualized as crucial steps in a program of research that is directed toward efficacy and effectiveness trials to answer pressing clinical problems, their value becomes more apparent, particularly to reviewers of grant proposals and papers.

There are several things that the ORBIT model is not. First, it is not prescriptive or restrictive. Rather, it identifies a flexible strategy for collecting a chain of evidence to enhance confidence that a promising behavioral treatment is ready for *Phase III* testing. The entire series of studies in the model could be conducted by a single investigator, a team, or, to save money and time, by integrating findings from multiple but unrelated investigators. By analogy, to build a house one could do everything alone or could serve in the role of an architect who creates the design but relies upon a team for construction, painting, plumbing, and electricity.

Second, the ORBIT model does not require that treatment development proceed precisely as specified in the framework, starting with *Phase Ia* and ending with *Phase IIb*. In many cases, a behavioral treatment already exists and the task is simply to adapt it to a new clinical problem, a new patient population, and/or a new outcome. In this case, the model could be used to decide what additional testing is needed. A small proof-of-concept study in a new patient population may show, for example, that results are promising but suboptimal, suggesting moving back to *Phase Ib* for refinement that could optimize results. In other cases, a new behavioral treatment may be so innovative and compelling that development is unnecessary and immediate testing in a feasibility pilot is warranted. The value of the ORBIT model lies in the provision of a framework that can facilitate decision-making in light of various situations and outcomes.

Third, the ORBIT model does not require evidence to be accrued for each "link" in the chain. For example, where well-established evidence exists linking a behavioral risk factor to a clinical outcome (e.g., evidence of an association between smoking and heart or lung disease), evidence from an efficacy trial that a behavioral treatment affects that behavioral risk factor (e.g., smoking) may be sufficient to influence clinical practice. In other cases, evidence of an intervention's effect on a *treatment target* may be adequate for proceeding to a clinical endpoint trial without evidence of the intervention's effect on a *behavioral risk factor*. An example is the use of biofeedback to treat chronic pain. Research using fMRI has shown that biofeedback can directly alter neural activity in specific brain regions and these changes can affect chronic clinical pain (deCharms et al., 2005). Here, one could move from evidence of an effect on the *treatment target* of brain activity (B) to a test of the efficacy of biofeedback on a *clinical outcome* (severity of pain) without evidence of the treatment's effect on an intervening *behavioral* risk factor (C).

Fourth, the ORBIT model does not require mechanisms and moderators to be included in all phases of behavioral treatment development. Although understanding the mechanisms through which an intervention produces its effects can be useful in developing better-targeted interventions, it is not critical to understand mechanisms of action in order to demonstrate an intervention's effectiveness (Blumenthal et al., 2002). In the ORBIT model, physiological mechanisms by which the behavioral risk factor translates into biomedical risk (referred to as biologic plausibility in epidemiology) can be focused on in early *Phase Ia* studies to help justify the choice of a behavioral risk factor and its cutpoint for clinical significance. Moreover, moderators (also called a priori subgroups in clinical trial methodology) can be studied in *Phase Ib* with the goal of adapting treatments so they are maximally powerful across all patients at risk. This can and should occur before the fixed protocol is tested in *Phase II*.

In summary, the ORBIT model is a systematic framework for guiding efforts to link behavioral solutions to clinical problems. Discoveries in the basic behavioral and social sciences hold great promise for addressing clinical health problems, yet there is no commonly established way to translate these findings into behavioral treatments. In the absence of industry support and regulatory guidelines, it is important for the behavioral science community to articulate and adopt models of behavioral treatment development that can facilitate the application of viable behavioral solutions to pressing health problems. Past models have emphasized the value of a systematic, phased approach to behavioral treatment development, and the recent emergence of evidence-based behavioral medicine (Davidson et al., 2002) provides clear standards for rigor. The ORBIT model complements and extends these efforts in proposing a systematic, well-defined process by which the investigator can achieve these rigorous standards.

Transparency of milestones for success in later phases of interventional research has been made possible by the required registration of trials in clinicaltrials.gov. An infrastructure to allow similar transparency in the earlier phases of behavioral treatment development is needed and perhaps can be facilitated by use of the ORBIT framework. Finally, because the ORBIT model focuses exclusively on the early phases of behavioral treatment development, further evolution of the model to deal with later phases of

translation is needed to achieve the ultimate goal of improving the utilization of proven behavioral treatments in clinical and community settings.

Currently, a window of opportunity exists in which demand is growing for primary and secondary prevention strategies that can reduce the burden of costly chronic diseases which have behavioral causes. This creates the need for a larger pool of effective behavioral treatments available for use in clinical care than currently exist. To take advantage of this opportunity, it is essential that investigators systematically build the rationale for a behavioral efficacy trial, conduct that efficacy trial, and, by so doing, build the evidence base for the value of behavioral treatments in clinical practice using the language of medicine and third-party payers. Creating a robust evidence base for the value of behavioral treatments in clinical care has enormous potential to expand choices for patients, improve quality of care, prevent or delay disease and disability, and, most urgently, lower health care costs not only for individual patients but for society as a whole.

References

Akesson, A., Larsson, S. C., Discacciati, A., & Wolk, A. (2014). Low-risk diet and lifestyle habits in the primary prevention of myocardial infarction in men: A population-based prospective cohort study. *Journal of the American College of Cardiology, 64,* 1299–1306.

Anderson, G. (2010). *Chronic care: Making the case for ongoing care*. Princeton, NJ: Robert Wood Johnson Foundation. Retrieved from www .rwjf.org/pr/product.jsp?id=50968

Appel, L. J., Champagne, C. M., Harsha, D. W., Cooper, L. S., Obarzanek, E., Elmer, P. J., . . . Young, D. R., & the Writing Group of the PREMIER Collaborative Research Group. (2003). Effects of comprehensive lifestyle modification on blood pressure control: Main results of the PREMIER clinical trial. *Journal of the American Medical Association, 289,* 2083–2093.

Appel, L. J., Clark, J. M., Yeh, H. C., Wang, N. Y., Coughlin, J. W., Daumit, G., . . . Brancati, F. L. (2011). Comparative effectiveness of weight-loss interventions in clinical practice. *The New England Journal of Medicine, 365,* 1959–1968. http://dx.doi.org/10.1056/NEJMoa1108660

Bartholomew, L., Parcel, G., Kok, G., Gottlieb, G., & Fernandez, M. E. (2011). *Planning health promotion programs: Intervention mapping*. San Francisco, CA: Jossey-Bass.

Blumenthal, J. A., Babyak, M., Wei, J., O'Connor, C., Waugh, R., Eisenstein, E., . . . Reed, G. (2002). Usefulness of psychosocial treatment of mental stress-induced myocardial ischemia in men. *The American Journal of Cardiology, 89,* 164–168. http://dx.doi.org/10.1016/S0002-9149(01)02194-4

Carroll, K. M., & Onken, L. S. (2005). Behavioral therapies for drug abuse. *The American Journal of Psychiatry, 162,* 1452–1460. http://dx.doi.org/10.1176/appi.ajp.162.8.1452

Chakraborty, B., Collins, L. M., Strecher, V. J., & Murphy, S. A. (2009). Developing multicomponent interventions using fractional factorial designs. *Statistics in Medicine, 28,* 2687–2708. http://dx.doi.org/10.1002/sim.3643

Chakravarty, E. F., Hubert, H. B., Krishnan, E., Bruce, B. B., Lingala, V. B., & Fries, J. F. (2012). Lifestyle risk factors predict disability and death in healthy aging adults. *The American Journal of Medicine, 125,* 190–197. http://dx.doi.org/10.1016/j.amjmed.2011.08.006

Coller, B. S. (2008). Translational research: Forging a new cultural identity. *The Mount Sinai Journal of Medicine, New York, 75,* 478–487. http://dx.doi.org/10.1002/msj.20064

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., & Petticrew, M. (2008a). Developing and evaluating complex interventions: The new

Medical Research Council guidance. *British Medical Journal, 337,* a1655. http://dx.doi.org/10.1136/bmj.a1655

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., & Petticrew, M. (2008b). *Developing and evaluating complex interventions: New guidance.* Retrieved from www.mrc.ac.uk/complexinterventionsguidance

Dallery, J., & Raiff, B. R. (2014). Optimizing behavioral health interventions with single-case designs: From development to dissemination. *Transitional Behavioral Medicine, 2014,* 1–14.

Davidson, K. W., Goldstein, M., Kaplan, R. M., Kaufmann, P. G., Knatterud, G. L., Orleans, C. T., . . . Whitlock, E. P. (2003). Evidence-based behavioral medicine: What is it and how do we achieve it? *Annals of Behavioral Medicine, 26,* 161–171. http://dx.doi.org/10.1207/S15324796ABM2603_01

deCharms, R. C., Maeda, F., Glover, G. H., Ludlow, D., Pauly, J. M., Soneji, D., . . . Mackey, S. C. (2005). Control over brain activation and pain learned by using real-time functional MRI. *Proceedings of the National Academy of Sciences of the United States of America, 102,* 18626–18631. http://dx.doi.org/10.1073/pnas.0505210102

Epstein, L. H., Paluch, R. A., Roemmich, J. N., & Beecher, M. D. (2007). Family-based obesity treatment, then and now: Twenty-five years of pediatric obesity treatment. *Health Psychology, 26,* 381–391. http://dx.doi.org/10.1037/0278-6133.26.4.381

Fagundo, A. B., de la Torre, R., Jiménez-Murcia, S., Agüera, Z., Granero, R., Tárrega, S., . . . Fernández-Aranda, F. (2012). Executive functions profile in extreme eating/weight conditions: From anorexia nervosa to obesity. *PLoS ONE, 7,* e43382. http://dx.doi.org/10.1371/journal.pone.0043382

Flay, B. R. (1986). Efficacy and effectiveness trials (and other phases of research) in the development of health promotion programs. *Preventive Medicine, 15,* 451–474. http://dx.doi.org/10.1016/0091-7435(86)90024-1

Freedland, K. E., Mohr, D. C., Davidson, K. W., & Schwartz, J. E. (2011). Usual and unusual care: Existing practice control groups in randomized controlled trials of behavioral interventions. *Psychosomatic Medicine, 73,* 323–335. http://dx.doi.org/10.1097/PSY.0b013e318218e1fb

Friedman, L. M., Furberg, C. D., & DeMets, D. L. (1998). *Fundamentals of Clinical Trials* (3rd ed.). New York, NY: Springer-Verlag. http://dx.doi.org/10.1007/978-1-4757-2915-3

Green, L. W. (1974). Toward cost-benefit evaluations of health education: Some concepts, methods, and examples. *Health Education Monographs, 2,* 34–64.

Greenwald, P., & Cullen, J. W. (1985). The new emphasis in cancer control. *Journal of the National Cancer Institute, 74,* 543–551.

Hamman, R. F., Wing, R. R., Edelstein, S. L., Lachin, J. M., Bray, G. A., Delahanty, L., . . . Wylie-Rosett, J., & the Diabetes Prevention Program Research Group. (2006). Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care, 29,* 2102–2107. http://dx.doi.org/10.2337/dc06-0560

Handelsman, Y., Mechanick, J. I., Blonde, L., Grunberger, G., Bloomgarden, Z. T., Bray, G. A., . . . Wyne, K. L., & the AACE Task Force for Developing Diabetes Comprehensive Care Plan. (2011). American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocrine Practice, 17*(Suppl 2), 1–53. http://dx.doi.org/10.4158/EP.17.S2.1

Jensen, M. D., Ryan, D. H., Apovian, C. M., Loria, C. M., Ard, J. D., Millen, B. E., . . . Yanovski, S. Z. (2013). 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. *Journal of the American College of Cardiology, 2014,* 65. http://dx.doi.org/10.1016/j.jacc.2013.11.004

Kazdin, A. (1982). *Single-case research designs: Methods for clinical and applied settings.* New York, NY: Oxford University Press. Retrieved from https://www.amazon.com/Single-Case-Research-Designs-Clinical-settings/dp/0195030206

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., & Nathan, D. M. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine, 346,* 393–403. http://dx.doi.org/10.1056/NEJMoa012512

Kraemer, H. C., Mintz, J., Noda, A., Tinklenberg, J., & Yesavage, J. A. (2006). Caution regarding the use of pilot studies to guide power calculations for study proposals. *Archives of General Psychiatry, 63,* 484–489. http://dx.doi.org/10.1001/archpsyc.63.5.484

Lei, H., Nahum-Shani, I., Lynch, K., Oslin, D., & Murphy, S. A. (2012). A "SMART" design for building individualized treatment sequences. *Annual Review of Clinical Psychology, 8,* 21–48. http://dx.doi.org/10.1146/annurev-clinpsy-032511-143152

Lipsky, M. S., & Sharp, L. K. (2001). From idea to market: The drug approval process. *The Journal of the American Board of Family Practice, 14,* 362–367.

Michie, S., van Stralen, M. M., & West, R. (2011). The behaviour change wheel: A new method for characterising and designing behaviour change interventions. *Implementation Science, 6,* 42. http://dx.doi.org/10.1186/1748-5908-6-42

Mohr, D. C., Spring, B., Freedland, K. E., Beckner, V., Arean, P., Hollon, S. D., . . . Kaplan, R. (2009). The selection and design of control conditions for randomized controlled trials of psychological interventions. *Psychotherapy and Psychosomatics, 78,* 275–284. http://dx.doi.org/10.1159/000228248

Mokdad, A. H., Marks, J. S., Stroup, D. F., & Gerberding, J. L. (2004). Actual causes of death in the United States, 2000. *Journal of the American Medical Association, 291,* 1238–1245. http://dx.doi.org/10.1001/jama.291.10.1238

Mozaffarian, D. (2014). The promise of lifestyle for cardiovascular health. *Journal of the American College of Cardiology, 64,* 1307–1309.

National Heart, Lung, and Blood Institute. (2008). *Translating basic behavioral and social science discoveries into interventions to reduce obesity: Centers for behavioral intervention development (U01).* Retrieved from http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-08-013.html

Navarro-Barrientos, J. E., Rivera, D. E., & Collins, L. M. (2011). A dynamical systems model for understanding behavioral interventions and body composition change. *Mathematical and Computer Modelling of Dynamical Systems, 17,* 183–203. http://dx.doi.org/10.1080/13873954.2010.520409

Office of Behavioral and Social Sciences Research. (2011). *Translating basic behavioral and social science discoveries into interventions to improve health-related behaviors (R01).* Retrieved from http://grants.nih.gov/grants/guide/pa-files/PA-11-063.html

Paganini-Hill, A., Kawas, C. H., & Corrada, M. M. (2011). Activities and mortality in the elderly: The Leisure World cohort study. *The Journals of Gerontology Series A, Biological Sciences and Medical Sciences, 66A,* 559–567. http://dx.doi.org/10.1093/gerona/glq237

Palmer, C. G., & Hadley, D. W. (2005). Evaluating the impact of genetic counseling and testing with signal detection methods. *Journal of Genetic Counseling, 14,* 17–27. http://dx.doi.org/10.1007/s10897-005-1497-4

Peterson, J. C., Czajkowski, S., Charlson, M. E., Link, A. R., Wells, M. T., Isen, A. M., . . . Jobe, J. B. (2013). Translating basic behavioral and social science research to clinical application: The EVOLVE mixed methods approach. *Journal of Consulting and Clinical Psychology, 81,* 217–230. http://dx.doi.org/10.1037/a0029909

Powell, L. H., Calvin, J. E., Jr., Mendes de Leon, C. F., Richardson, D., Grady, K. L., Flynn, K. J., . . . Eaton, C., & the Heart Failure Adherence and Retention Trial Investigators. (2008). The Heart Failure Adherence and Retention Trial (HART): Design and rationale. *American Heart Journal, 156,* 452–460. http://dx.doi.org/10.1016/j.ahj.2008.05.011

Ridenour, T. A., Pineo, T. Z., Maldonado Molina, M. M., & Hassmiller Lich, K. (2013). Toward rigorous idiographic research in prevention

science: Comparison between three analytic strategies for testing preventive intervention in very small samples. *Prevention Science, 14,* 267–278. http://dx.doi.org/10.1007/s11121-012-0311-4

Rounsaville, B. J., Carroll, K. M., & Onken, L. S. (2001). A stage model of behavioral therapies research: Getting started and moving on from Stage I. *Clinical Psychology: Science and Practice, 8,* 133–142. http://dx.doi.org/10.1093/clipsy.8.2.133

Schroeder, S. A. (2007). Shattuck lecture. We can do better—Improving the health of the American people. *The New England Journal of Medicine, 357,* 1221–1228. http://dx.doi.org/10.1056/NEJMsa073350

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Review of Clinical Psychology, 4,* 1–32. http://dx.doi.org/10.1146/annurev.clinpsy.3.022806.091415

Stevens, J., Taber, D. R., Murray, D. M., & Ward, D. S. (2007). Advances and controversies in the design of obesity prevention trials. *Obesity, 15,* 2163–2170. http://dx.doi.org/10.1038/oby.2007.257

Strolla, L. O., Gans, K. M., & Risica, P. M. (2006). Using qualitative and quantitative formative research to develop tailored nutrition intervention materials for a diverse low-income audience. *Health Education Research, 21,* 465–476. http://dx.doi.org/10.1093/her/cyh072

Wadden, T. A., Volger, S., Sarwer, D. B., Vetter, M. L., Tsai, A. G., Berkowitz, R. I., . . . Moore, R. H. (2011). A two-year randomized trial of obesity treatment in primary care practice. *The New England Journal of Medicine, 365,* 1969–1979. http://dx.doi.org/10.1056/NEJMoa1109220

Wansink, B. (2010, December). *Designing interventions that stick: Behavioral event monitoring.* Presented at NIH Workshop on "Translating Ideas into Interventions: The Process of Developing Behavorial Interventions." Bethesda, MD. Retrieved from http://www.nihorbit.org/ORBIT%20Content/Workshops%20and%20Conferences.aspx?PageView=Shared

Yoon, P. W., Bastian, B., Anderson, R. N., Collins, J. L., Jaffe, H. W., & the Centers for Disease Control and Prevention (CDC). (2014, May 2). Potentially preventable deaths from the five leading causes of death—United States, 2008–2010. *Morbidity and Mortality Weekly Report, 63,* 369–374.

Zucker, D. R., Ruthazer, R., & Schmid, C. H. (2010). Individual (N-of-1) trials can be combined to give population comparative treatment effect estimates: Methodologic considerations. *Journal of Clinical Epidemiology, 63,* 1312–1323. http://dx.doi.org/10.1016/j.jclinepi.2010.04.020