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Linda M. Collins · Kari C. Kugler
*Editors*

# Optimization of Behavioral, Biobehavioral, and Biomedical Interventions

## Advanced Topics

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# Preface

Behavioral, biobehavioral, and biomedical interventions play an important role in society worldwide. These interventions are aimed at, for example, helping people quit smoking; improving reading skills in children; helping autistic children learn how to communicate verbally; improving family functioning; keeping convicted criminals who have served their time from engaging in criminal activity; treating cancer, diabetes, depression, and many other diseases and health problems; slowing the progression of heart failure; preventing the onset of drug abuse; and improving treatment regimen compliance in people living with HIV. These are just a few of many, many examples.

This book and another book, titled *Optimization of Behavioral, Biobehavioral, and Biomedical Interventions: The Multiphase Optimization Strategy (MOST)* (Collins, 2018), are companion volumes. Both are focused on MOST, an engineering-inspired framework for arriving at and then evaluating an optimized intervention. The objective is to develop an intervention that is not only effective but also efficient, economical, and scalable. MOST consists of three phases: preparation, optimization, and evaluation. Activities in the preparation phase include selection of the components that are candidates for inclusion in the intervention and development of a detailed conceptual model of the process to be intervened upon. In the preparation phase, the investigator also specifies an optimization criterion. This criterion operationalizes the goal of optimization. For example, if it has been established that to be scalable a particular intervention must cost no more than $400 per participant to implement, an appropriate optimization criterion would be "the most effective intervention that can be obtained for no more than $400 per participant in implementation costs." In the optimization phase, which occurs before an intervention is evaluated in an RCT, one or more optimization trials are conducted to gather information on the individual and combined effects of the candidate components. This information, along with the optimization criterion, forms the basis for selection of the components and component levels that make up the optimized intervention. The optimization trial may use any of a wide variety of experimental designs and approaches, depending on the type of intervention to be optimized, the precise research questions that are of interest, and the circumstances.

In the evaluation phase, the effectiveness of the optimized intervention is confirmed in a standard RCT. If the optimization criterion was appropriately specified, the resulting intervention will be immediately scalable.

Collins (2018) provides a comprehensive introduction to MOST. In addition to an overview of MOST, the book includes information on developing a conceptual model; using factorial and fractional factorial designs in optimization trials, with an entire chapter devoted to interactions; applying the resource management principle when selecting an experimental design; making decisions about selection of components and component levels based on experimental results; and numerous other topics. The book also includes a chapter introducing adaptive interventions.

Early in the process of planning a book about MOST, it became clear that a number of topics would need to be covered to arrive at a comprehensive treatment. An in-depth treatment of the process of arriving at a conceptual model was needed. Investigators wanting to conduct factorial optimization trials were asking for practical advice about implementing large and complex experiments in field settings. Intervention scientists who worked in populations with a cluster structure, such as educational researchers, had been asking whether and how they could appropriately conduct optimization trials. Clarification was needed on approaches such as the SMART experimental design and system identification experiments, and how they fit into the MOST framework. There was perennial confusion about the difference between conducting a factorial ANOVA using effect coding and using dummy coding. It seemed natural that cost-effectiveness could be a consideration in the optimization phase of MOST, but it was not apparent how. Guidance was needed on how to take advantage of the possibilities for interesting mediation analyses opened up by factorial optimization trials.

Linda Collins was not an expert in many of these topics, and it was clear that other authors would be able to do a much better job of presenting them. An edited book, with chapters written by experts in each area, was needed in addition to an authored book. Dr. Kari Kugler agreed to serve with Dr. Collins as coeditor. The editors were extremely fortunate that a number of outstanding academics agreed to contribute chapters.

## The Chapters in This Book

The first chapter, by Kugler, Wyrick, Tanner, Milroy, Chambers, Ma, Guastaferro, and Collins, describes a critically important, but too often overlooked, aspect of intervention optimization: the development of a detailed and highly specific conceptual model. Specification of a conceptual model is often a demanding and challenging task, requiring the integration of a diverse body of scientific literature and input from many members of the research team. However, it is worth the time and effort, because it is ultimately rewarding to arrive at a sophisticated conceptual model that will provide a firm conceptual foundation for the remainder of the preparation phase as well as the optimization and evaluation phases of MOST.

The chapter "Using the Multiphase Optimization Strategy (MOST) to Develop an Optimized Online STI Preventive Intervention Aimed at College Students: Description of Conceptual Model and Iterative Approach to Optimization" also introduces the idea of taking an iterative approach to optimization. In this approach, successive optimization trials are performed, with the objective of improving the intervention by revising or replacing weak or inert components and re-testing the components.

Readers who would like to use MOST in their work but are uneasy about implementation of an experiment that can be much more complex than an RCT will find that the chapter "Implementing Factorial Experiments in Real-World Settings: Lessons Learned While Engineering an Optimized Smoking Cessation Treatment" provides a wealth of valuable information. For nearly 10 years, Piper, Schlam, Fraser, Oguss, and Cook have successfully conducted factorial optimization trials in ordinary health care settings. In this chapter, they offer practical advice and lessons learned based on their extensive experience in the implementation of large factorial optimization trials in real-world field settings. Piper et al. discuss going from selection of intervention components to a workable experimental design; maintaining a high level of fidelity when conducting a complex experiment in the field; conducting random assignment with as many as 32 experimental conditions; and other considerations of particular interest to scientists who are relatively new to MOST. The chapter "Implementing Factorial Experiments in Real-World Settings: Lessons Learned While Engineering an Optimized Smoking Cessation Treatment" will be helpful to readers who would like to know how to implement large factorial experiments in field settings successfully and with few protocol deviations.

The chapter "Multilevel Factorial Designs in Intervention Development," by Nahum-Shani and Dziak, discusses design of optimization trials, statistical power, and analysis of the resulting data when there is a multilevel (also called hierarchical, cluster, or nested) structure. A multilevel structure can occur naturally when experimental subjects are grouped in schools, neighborhoods, clinics, families, or some other unit. A multilevel structure can also be induced by the experimenter, for example, if part of the experiment involves assigning individuals to some kind of group-delivered treatment. The presence of a multilevel structure has different implications for experimental design, data analysis, and statistical power depending on whether the clustering is naturally occurring or experimenter-induced and whether individuals or entire clusters are to be randomly assigned to experimental conditions. Nahum-Shani and Dziak provide a careful and comprehensive review that will help investigators decide on the best way to conduct an optimization trial when a multilevel structure must be considered. This chapter may be of particular interest to scientists developing educational or other school-based interventions.

In an adaptive intervention, the intervention content, dose, or approach can be varied across participants and across time, with the objective of achieving or maintaining a good outcome for all participants (see Chapter 8 in the companion volume). Adaptive interventions range in intensity of adaptation. In low-intensity adaptive interventions, the content, dose, or approach is varied only a few times, or adaptation occurs infrequently. In the chapter "Experimental Designs for Research on Adaptive Interventions: Singly and Sequentially Randomized Trials," Almirall, Nahum-Shani, Wang, and Kasari discuss the design of optimization trials when the objective is optimization of a low-intensity adaptive intervention. Almirall et al. demonstrate that a variety of experimental designs can be appropriate and remind the reader that the choice of design must be based on the precise scientific questions motivating the experiment. This chapter reviews a number of experimental design alternatives, including types of singly randomized trials and sequential, multiple assignment, randomized trials (SMARTs), most of which are variations on the factorial experiment.

In contrast to low-intensity adaptive interventions, intensively adaptive interventions may vary the content, dose, or approach frequently, for example, daily or even several times per day. For example, mhealth interventions, in which the intervention is delivered via a mobile device app, are often intensively adaptive. In the chapter "Intensively Adaptive Interventions Using Control Systems Engineering: Two Illustrative Examples," Rivera, Hekler, Savage, and Downs discuss one approach to design of optimization trials when the objective is to optimize an intensively adaptive intervention. Their approach is not a variation on the factorial experiment. Instead, these authors take a control engineering perspective. From this perspective, the outcome, along with the behaviors and other factors that influence the outcome, is considered a dynamical system, and the adaptive intervention is a controller that can be used to modulate this system. Then the optimization trial is a system identification experiment, which provides the data needed to develop the controller. This chapter will appeal both to behavioral scientists considering using control engineering principles in their work and to engineers who may be interested in applying their skill set in the behavioral sciences.

Once an optimization trial has been conducted, the data need to be analyzed properly so that the results can be used in making decisions about which components and component levels will make up the optimized intervention. In the companion volume, Collins recommended using effect coding rather than dummy coding when analyzing data from a factorial optimization trial. However, dummy coding is more familiar to many behavioral scientists. In the chapter "Coding and Interpretation of Effects in Analysis of Data from a Factorial Experiment," Kugler, Dziak, and Trail compare and contrast effect coding and dummy coding of factorial experiments. They demonstrate that in most cases, effect coding and dummy coding produce different estimates of individual effects (although the omnibus $F$ will be identical). They also explain that effect coding models effects that correspond to the definitions of analysis of variance (ANOVA) main effects and interactions that appear in most statistics textbooks, whereas in general dummy coding models a different set of effects. The chapter "Coding and Interpretation of Effects in Analysis of Data from a Factorial Experiment" will clarify this important issue for data analysts and help the reader to see why effect coding is usually a better choice for analysis of data from an optimization trial.

In the companion volume, several different possible goals for optimization are discussed, with the emphasis on seeking the most effective intervention that can be obtained subject to a specified fixed upper limit on cost. However, in many situations it may be desired to use the results of the optimization trial along with data on cost to identify the set of components and component levels that represents the most cost-effective intervention. This requires a more sophisticated approach to making decisions about selection of components and component levels; at this writing, there are still many unanswered questions about how to accomplish this. In the chapter "Optimizing the Cost-Effectiveness of a Multicomponent Intervention Using Data from a Factorial Experiment: Considerations, Open Questions, and Tradeoffs Among Multiple Outcomes," Dziak discusses issues and open research areas related to cost-effectiveness and MOST.

Optimization trials yield rich data that can form the basis for interesting and informative secondary analyses. The final chapter, "Investigating an Intervention's Causal Story: Mediation Analysis Using a Factorial Experiment and Multiple Mediators," discusses one type of secondary analysis of a factorial optimization trial, mediation analysis. The majority of readers of this book will have some familiarity with mediation analysis of data from an RCT. The purpose of such analyses is to determine which variables mediated any observed treatment effect, and thereby obtain an empirical sense of the mechanisms underlying the intervention. Mediation analysis of data from a two-arm RCT can be highly informative. However, because in an RCT the treatment is an aggregate of all the components, it is not possible to determine which variables mediate which individual components. Smith, Coffman, and Zhu review the possibilities that are opened up by mediation analysis of data when the treatment is a factorial experiment rather than a two-arm RCT. Here it is possible to model mediation of the effect of a single factor, and even to model mediation of an interaction effect! Mediation analysis of the data from a factorial optimization trial can be helpful in the optimization phase of MOST and is likely to be particularly helpful in informing the preparation phase of a subsequent cycle of MOST.

## How to Use This Book

From the beginning, the objective was that the two companion volumes would be tightly integrated. The reader will see that each book cites the other repeatedly. Moreover, the chapters in the present book assume an understanding of the material in Collins (2018), so it is a good idea to have read that book before reading this one. Each chapter in this book stands alone, and, unlike the chapters in the companion volume, it is not necessary to read them in the order they appear.

The eight chapters in this book have been presented according to roughly where they fall in the MOST process. The first two chapters discuss matters pertaining primarily to the preparation phase of MOST and the early part of the optimization phase, and the remaining chapters pertain to designing an optimization trial, conducting primary data analysis, selecting components and component levels, and conducting secondary analysis of data from an optimization trial. The material in the Smith et al. chapter could also be considered part of the preparation phase, because mediation analyses are an excellent source of information useful in updating and refining a conceptual model. This may be done in preparation for a subsequent round of optimization aimed at further improvements to the intervention.

Intervention scientists often work in teams, and different team members may have different roles. For a scientist whose role is primarily intervention development, chapters "Using the Multiphase Optimization Strategy (MOST) to Develop an Optimized Online STI Preventive Intervention Aimed at College Students: Description of Conceptual Model and Iterative Approach to Optimization" and "Optimizing the Cost-Effectiveness of a Multicomponent Intervention Using Data from a Factorial Experiment: Considerations, Open Questions, and Tradeoffs Among Multiple Outcomes" may be of particular interest. For a team member responsible for implementation, the chapter "Implementing Factorial Experiments in Real-World Settings: Lessons Learned While Engineering an Optimized Smoking Cessation Treatment" is essential reading. The chapters "Multilevel Factorial Designs in Intervention Development," "Experimental Designs for Research on Adaptive Interventions: Singly and Sequentially Randomized Trials," and "Intensively Adaptive Interventions Using Control Systems Engineering: Two Illustrative Examples" were written to be helpful to those responsible for selecting the design of the optimization trial. Those chapters, along with chapters "Coding and Interpretation of Effects in Analysis of Data from a Factorial Experiment" and "Investigating an Intervention's Causal Story: Mediation Analysis Using a Factorial Experiment and Multiple Mediators," are likely to be interesting to a statistician, methodologist, or data analyst.

We hope you find this book and its companion helpful and that you have an opportunity to use MOST in your work.

University Park, PA
2018

Linda M. Collins
Kari C. Kugler

# Contents

# Using the Multiphase Optimization Strategy (MOST) to Develop an Optimized Online STI Preventive Intervention Aimed at College Students: Description of Conceptual Model and Iterative Approach to Optimization

**Kari C. Kugler, David L. Wyrick, Amanda E. Tanner, Jeffrey J. Milroy, Brittany Chambers, Alice Ma, Kate M. Guastaferro, and Linda M. Collins**

**Abstract** This chapter describes some aspects of an application of the multiphase optimization strategy (MOST) to optimize and evaluate itMatters, an online intervention that targets the intersection of alcohol use and sexual behaviors to reduce sexually transmitted infections (STIs) among college students. The chapter emphasizes two aspects of this application. First, we describe the development of a detailed conceptual model during the preparation phase of MOST. This conceptual model guided decisions such as the choice of outcome variables. Second, we describe an iterative approach to experimentation during the optimization phase of MOST. The objective of the iterative approach is to build a highly effective intervention by using repeated optimization trials to evaluate which intervention components meet a given criterion for effectiveness and which do not. Revisions are undertaken to improve the components that do not meet the criterion, and then a

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subsequent optimization trial is used to reevaluate the components. This iterative approach has the potential to enable the investigator to develop more effective, efficient, economical, and scalable interventions.

## 1 Introduction

Approximately 70% of college students are sexually experienced, yet only half of sexually active students report using a condom during their last sexual encounter, and 75% report inconsistent or no condom use (American College Health Association, 2016). Concurrent and casual sexual partnerships are also common among college students (Olmstead, Pasley, & Fincham, 2013), with one third reporting not using a condom during a penetrative hookup (Fielder & Carey, 2010); a hookup is a casual sexual encounter without the expectation of dating or a romantic relationship (Garcia, Reiber, Massey, & Merriwether, 2012). Inconsistent condom use (Trepka et al., 2008); multiple, concurrent partners (Lewis, Miguez-Burban, & Malow, 2009); and penetrative hookups (Paul, McManus, & Hayes, 2000) are all high-risk behaviors that contribute to the high prevalence of sexually transmitted infections (STIs) among college students (Kann et al., 2016). Drinking alcohol is a known risk factor for unprotected sex, particularly among college students, and, by extension, a risk factor for exposure to STIs. An extensive body of research (Scott-Sheldon et al., 2016; Shuper et al., 2010) has documented a consistently strong and positive, but also complex, relationship between alcohol use and unprotected sex (Ebel-Lam, MacDonald, Zanna, & Fong, 2009; Prause, Staley, & Finn, 2011; Shuper et al., 2010).

Numerous individual-level interventions for college students have been developed that focus separately on alcohol use (Carey, Scott-Sheldon, Elliot, Bolles, & Carey, 2009) and condom use (Scott-Sheldon, Huedo-Medina, Warren, Johnson, & Carey, 2011), but few have directly emphasized the alcohol-sex relationship. Dermen and Thomas (2011) found that a brief intervention combining alcohol risk-reduction content with HIV risk-reduction content produced effects on sexual risk behaviors (e.g., frequency of unprotected sex), but not on alcohol use frequency or intensity. Lewis and colleagues (2014) found that the use of personalized normative feedback specific to drinking in sexual situations was effective at reducing alcohol use and sexual risk behaviors (e.g., drinking alcohol prior to or during sex).

Although these studies suggest that interventions focusing on the alcohol-sex relationship show promise, more research is needed to overcome some limitations. For example, the study by Dermen and Thomas (2011) was based on a relatively small sample of predominately White students. Lewis and colleagues (2014) included only sexually active students with minimal levels of drinking behavior and focused solely on challenging normative misperceptions. It is unclear whether the findings would generalize to a more diverse population with a wider range of sexual experiences and drinking behaviors. It is also unclear whether an intervention would be more effective if it targeted other constructs beyond correcting normative misperceptions.

Thus there is a need for development of an effective STI preventive intervention that targets the intersection of alcohol use and sexual risk behaviors and is aimed at a diverse population of college students. This chapter describes an ongoing study that is attempting to accomplish this aim by developing an online intervention called itMatters. The objective of itMatters is to prevent STIs in college students by focusing on the intersection of alcohol use and sexual risk behaviors. We are applying the multiphase optimization strategy (MOST) to develop, optimize, and evaluate itMatters.

MOST is an engineering-inspired framework for building more effective, efficient, economical, and scalable interventions. MOST includes three phases: preparation, optimization, and evaluation. As part of the preparation phase, a carefully specified, theoretically driven conceptual model is established to articulate how each component that is a candidate for inclusion in the intervention is hypothesized to affect the outcome. During the optimization phase, the effectiveness of the individual intervention components is examined experimentally. Based on the information obtained via this experimentation, the components and component levels that make up the optimized intervention are selected. In the evaluation phase, the resulting optimized intervention is evaluated using a standard RCT.

MOST has been applied to develop interventions in a wide range of health areas, including school-based prevention of alcohol and drug use and HIV (Caldwell et al., 2012), drug use among NCAA athletes (Wyrick, Rulison, Fearnow-Kenney, Milroy, & Collins, 2014), smoking cessation (e.g., Baker et al., 2016), weight loss (Pellegrini, Hoffman, Collins, & Spring, 2014, 2015), and cardiology (Huffman et al., 2017). For a more detailed description of MOST, see the companion volume (Collins, 2018).

## *1.1 The Current Chapter*

The purpose of the current chapter is to describe our application of MOST to optimize and evaluate the itMatters intervention. The chapter emphasizes two aspects of this application. First, we describe the development of a detailed conceptual model during the preparation phase of MOST (see Chapter 2 in the companion volume). Second, we describe an iterative approach to experimentation during the optimization phase of MOST. The objective of the iterative approach is to build a highly effective intervention by using repeated optimization trials to evaluate which intervention components meet a given criterion for effectiveness and which do not. Revisions are undertaken to improve the components that do not meet the criterion, and then a subsequent optimization trial is used to reevaluate the components.

# 2 The Conceptual Model of the Intersection of Alcohol Use and Sexual Behaviors

## *2.1 Overview*

During the preparation phase of MOST, a carefully specified, theoretically driven conceptual model is articulated. As noted in the companion volume, the purpose of the conceptual model is to express "all of what is known or hypothesized about how the intervention under development is to intervene on the behavioral, biobehavioral, or biomedical process" (Collins, 2018, p. 64). In other words, the conceptual model forms the basis for the intervention by specifying the set of components that are candidates for inclusion in the intervention, identifying the proximal mediators that are immediate targets of each component, and outlining the causal pathways by which these candidate intervention components are intended to have an impact on the proximal and distal outcomes.

The conceptual model that forms the basis of the itMatters intervention expresses how alcohol use is hypothesized to lead to sexual risk behaviors (e.g., unprotected sex, penetrative hookups) and how this increases the risk for STIs among college students. Because examination of the intersection of alcohol use and sex has been limited primarily to laboratory studies (Davis et al., 2014; George et al., 2009; Prause et al., 2011), this conceptual model has been informed by empirical research and behavioral theory on alcohol use and sexual risk behaviors separately and together.

The itMatters conceptual model is depicted in Fig. 1. The purpose of Fig. 1 is to provide a visual representation of how the intervention components are hypothesized to prevent alcohol-related sexual risk behaviors and, ultimately, STIs. As the figure suggests, a conceptual model is similar to a logic model but goes a step further by detailing the mechanisms by which each intervention component is expected to effect change in the primary outcome(s) (see Chapter 2 in the companion volume for more detail).

Before examining Fig. 1 in more detail, it is necessary to define two terms. The first is protective behavioral strategies (PBS). In this case, PBS are approaches an individual uses to reduce the potentially negative consequences associated with alcohol-related sexual risk behaviors (Treloar, Martens, & McCarthy, 2015). Examples of PBS include limiting alcohol intake; using a condom, including making sure they are readily available and that the skills needed to use them properly have been acquired; designating a friend to step in if an individual appears headed for excessive alcohol use or an unintended sexual encounter; and proactively sharing sexual boundaries with a partner.

The second term to be defined is myopic effects. Myopic effects are cognitive effects of alcohol that affect an individual's appraisal of sex potential and risk (Sevincer & Oettingen, 2014). In particular, alcohol use leads to cognitive impairment that can affect decision-making and lead to a higher probability of risk-taking. Alcohol myopia theory (Sevincer & Oettingen, 2014) helps explain this.

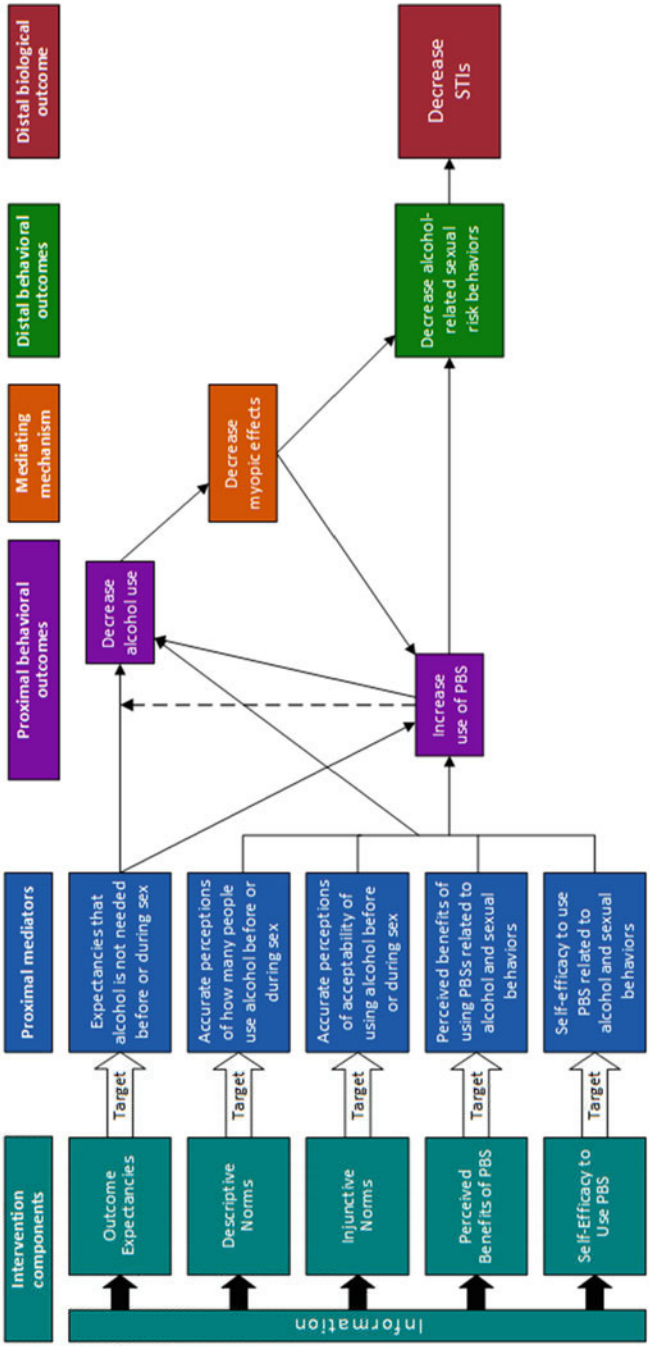


**Fig. 1** Conceptual model for a behavioral intervention to reduce sexually transmitted infections (STIs) among college students. PBS stands for protective behavioral strategies

Alcohol myopia theory posits that alcohol increases a person's concentration on the immediate situation (e.g., enjoyment), limits higher-level cognitive functioning, and reduces attention on more distant events or cues (e.g., reducing the risk of unprotected sex); these effects are intensified as the quantity or dose of alcohol increases (Dry, Burns, Nettelbeck, Farquharson, & White, 2012). As suggested by this theory, the mechanism of how alcohol use affects sexual behaviors is further influenced by several factors, such as primary (e.g., sex potential) and secondary (e.g., STI risk) appraisals, which are anticipated to influence alcohol-related sexual behaviors directly (Purdie et al., 2011) and indirectly through PBS strategies (Abbey, Saenz, & Buck, 2005).

Examining Fig. 1 from left to right shows how each component targets a particular putative proximal mediator (henceforth termed proximal mediator). These proximal mediators, in turn, affect their respective proximal behavioral outcomes: they reduce alcohol use and increase the use of PBS. A decrease in alcohol use leads to a decrease in myopic effects, which decreases the likelihood of engaging in alcohol-related sexual risk behaviors directly and indirectly by increasing the likelihood of using PBS. Increased use of PBS leads to a decrease in the likelihood of engaging in alcohol-related sexual risk behavior.

Figure 1 is not a structural equation modeling diagram, although it resembles one in some ways. One important difference is that Fig. 1 is meant to convey the rationale for the intervention, not provide a summary of how data would be analyzed. For this reason, the figure does not contain an arrow representing every anticipated nonzero regression coefficient. Another difference is that some of the boxes represent an increase or decrease in a variable. This is not always a feature of figures representing conceptual models. We used this approach here to avoid complicating the figure with negative signs on some paths.

## *2.2 Intervention Components*

Figure 1 shows six components. One component, information, is represented by a bar on the far left of the figure to indicate that information is considered a necessary foundation for the other components. The information component will not be examined experimentally during the optimization phase. Because this material is foundational to the remaining components, an a priori decision has been made to include it in the intervention. All experimental subjects will be provided with the information component. The remaining five components are candidates for inclusion in itMatters and therefore will be examined experimentally. These are listed in the left-hand area of Fig. 1. Each is labeled with a brief name of the proximal mediator it targets: outcome expectancies, descriptive norms, injunctive norms, perceived benefits of PBS, and self-efficacy to use PBS. The arrow labeled Target indicates the immediate target of each component. (Note that even though each component is connected by an arrow only to the mediator it directly targets, a component may have an effect on other mediators. As mentioned previously, the purpose of Fig. 1 is to depict the reason why a component is a candidate for inclusion in the intervention, not to show every possible nonzero path.) Figure 1 specifies the hypothesized causal pathways of the effect of each of these intervention components on the proximal behavioral outcomes (i.e., alcohol use, use of PBS), the distal behavioral outcome (i.e., alcohol-related sexual risk behaviors), and the distal biological outcome, STIs, via the proximal mediators. A detailed description of the pathways is provided below. First, we review each candidate component.

### 2.2.1 Outcome Expectancies

Informed by expectancy theory (Jones, Corbin, & Fromme, 2001), this component challenges positive expectancies related to alcohol use before or during sex, such as expectancies that using alcohol will increase the likelihood of engaging in sex (Davis et al., 2010). Thus, the component is designed to convince participants that no, or at most limited, alcohol use is needed before or during sex. Outcome expectancies are consistently associated with behavioral outcomes, with positive expectancies associated with an increased likelihood of alcohol consumption (Davis et al., 2010) and a decrease in PBS (Logan, Koo, Kilmer, Blayney, & Lewis, 2015). There is a notable moderating effect by the use of PBS.

Grazioli and colleagues (2015) found that the association between expectancies and alcohol use was weaker for students with a high use of PBS (e.g., predetermined strategies to limit or stop drinking). This implies an interaction between PBS and the outcome expectancies proximal mediator. This is represented by a dashed line in Fig. 1 running from the box representing PBS to the line representing the relation between outcome expectancies and alcohol use.

### 2.2.2 Descriptive Norms and Injunctive Norms

Two different types of social norms, descriptive (perceived prevalence of a behavior; social norms theory (Berkowitz, 2004)) and injunctive (perceived peer approval of a behavior (Ajzen, 1991)), are positively associated with alcohol use (Reid & Carey, 2015) and inversely associated with PBSs (Lewis, Rees, Logan, Kaysen, & Kilmer, 2010). For example, perceptions that participating in sexual behaviors while under the influence of alcohol is prevalent (descriptive norms) and is approved of by one's peers (injunctive norms) increase the likelihood of using alcohol and decrease the use of PBS. However, a recent study by Lewis and colleagues (2014) found that, although college students tend to underestimate the prevalence of protective behaviors (e.g., condom use) and overestimate the prevalence of risk behaviors (e.g., drinking prior to sex), only norms pertaining to the overestimation of sexual risk behaviors (i.e., descriptive norms) are related to actual behavior.

### 2.2.3 Perceived Benefits

According to the health belief model (Rosenstock, 1990), perceived benefits of using PBS to reduce the negative consequences of using alcohol or having sex are expected to have an impact on both alcohol use and use of PBS. Although there is evidence to support the idea that perceived benefits of using PBS reduce alcohol consumption (Pearson, 2013), there is less empirical evidence that perceived benefits of using PBS lead to an actual increase in use of PBS. Thus, inclusion of this component is more supported theoretically than empirically. Nevertheless, we hypothesize that increasing perceived benefits of using PBS will lead to decreased alcohol use and increased use of PBS.

### 2.2.4 Self-Efficacy to Use PBS

This component is designed to increase self-efficacy to use PBS. Self-efficacy (Bandura, 1977) for using PBS such as limiting alcohol intake or planning to discuss sexual boundaries with a partner when intoxicated is expected to decrease alcohol use (Pearson, Prince, & Bravo, 2017) and increase the use of PBS. In a study specifically about alcohol use, Ehret, Ghaidarov, and LaBrie (2013) found that drinking refusal self-efficacy was associated with decreased weekly alcohol use. In a study focused on sexual risk behaviors, Nesoff, Dunkle, and Lang (2016) found that condom use negotiation skills were positively associated with condom use.

## *2.3 Pathways from the Intervention Components to Alcohol-Related Sexual Risk Behaviors and STIs*

Figure 1 shows that each component targets one of the proximal mediators. In turn, each mediator is hypothesized to produce an effect on the proximal behavioral outcomes, that is, a reduction in alcohol use and an increase in the use of PBS. Two main pathways lead to a reduction in alcohol-related sexual risk behaviors and a reduction in STIs, each associated with one of the proximal behavioral outcomes. Reducing alcohol use leads to a decrease in myopic effects and also to an increase in the use of PBS, both of which lead to a decrease in alcohol-related sexual risk behaviors. The increased use of PBS can itself decrease alcohol use (and then the subsequent pathway to alcohol-related sexual risk behaviors can be followed as described above), and it can directly decrease the use of alcohol-related sexual risk behaviors. For example, even without reducing alcohol intake, a student could be sure to use a condom as appropriate in any sexual encounter. In this case, even though the sexual encounter may be alcohol-related, its risk is greatly reduced.

## 2.4 Potential Moderators

We do not make specific hypotheses about moderators, but we note a number of potential moderators that will be examined in data analysis. They are not included in the conceptual model because we chose to develop a model focusing specifically on how the candidate intervention components are hypothesized to have an effect on the proximal mediators, proximal behavioral outcomes, and distal biological outcomes. However, we include a description of potential moderators here for completeness.

### 2.4.1 Gender

Gender differences in alcohol use and sexual behaviors are well documented. For example, males report higher participation in heavy episodic drinking in the past 30 days (American College Health Association, 2016) and typically report higher levels of specific sexual behaviors than females (e.g., more lifetime sexual partners; (Chandra, Copen, & Mosher, 2013)). Males and females report comparable numbers of hookups, yet males report more penetrative behaviors during a hookup (i.e., vaginal and anal sex) than females. Fisher (2009) suggests that this may be due to reporting bias that is a by-product of the social desirability of penetrative behaviors among males. Further, in a study by Kirmani and Suman (2010), males reported more positive norms for engaging in sexual behaviors and more positive alcohol- and sex-related expectancies than females. Although these differences are important, they are not expected to moderate either component effects or the effects of mediators. The itMatters intervention components have been developed to work equally well for both males and females. Although we hypothesize that there will be no gender-by-component interactions, we will explore this interaction empirically.

### 2.4.2 Race/Ethnicity

Notable race/ethnicity differences have been observed in alcohol use and sexual risk behaviors. Although African American/Black and Hispanic/Latino students typically report lower alcohol use than White students (Paves, Pedersen, Hummer, & Labrie, 2012), Black and Latino students report more unprotected sex and more partners than White students (Randolph, Torres, Gore-Felton, Lloyd, & McGarvey, 2009) and carry a disproportionate STI burden (Centers for Disease Control and Prevention, 2013). This disparity is often attributed to the gender ratio (more females than males on campus) and available sex partner pools on college campuses, particularly at historically black colleges and universities (Ferguson, Quinn, Eng, & Sandelowski, 2006; Jennings et al., 2010). Thus the association between self-efficacy and use of PBS might be weaker for Black students than White students:

Black women may perceive less power to negotiate condom use and discuss safer sex openly due to fear of losing a male partner to another woman.

#### 2.4.3 Other Individual-Level

Another possible moderator is individual differences in sexual sensation-seeking. Individuals who are high in sexual sensation-seeking are expected to experience a more negative impact of the effects of alcohol (e.g., reduced condom use and increased penetrative hookups) than those who are lower in sexual sensation-seeking (Hendershot, Stoner, George, & Norris, 2007). Relational factors may moderate the association between the use of PBS and alcohol-related sexual risk behaviors. For example, the association between negotiating condom use and using a condom is weaker for individuals in a committed relationship than those in a casual relationship (Brown & Vanable, 2007) and weaker when a sexual partner is 3 or more years older compared to less than 3 years older (Ford, Sohn, & Lepkowski, 2001). In addition, the association is weaker if there is a reliance on hormonal contraception versus a barrier method such as a condom (Bailey, Fleming, Catalano, Haggerty, & Manhart, 2012).

#### 2.4.4 Environmental

There is less scientific literature on environmental moderators between the proximal mediators and distal behaviors among college students. However, we hypothesize the association between accurate perceptions of descriptive norms, and behavioral outcomes is weaker when a Greek system exists on campus than not, and we hypothesize that the association between having a plan to use condoms (a PBS) and using condoms is stronger if free condoms are available on campus (Reeves, Ickes, & Mark, 2016).

## 3 Optimizing itMatters

### *3.1 Overview of the Iterative Approach to Optimization*

The goal of the current study is to build an effective and efficient STI preventive intervention. By effective intervention, we mean an intervention that has been empirically demonstrated to decrease alcohol-related sexual risk behaviors and, ultimately, STIs. By efficient intervention, we mean an intervention that is made up exclusively of components that have empirically detectable effects on the proximal mediators. In other words, we plan to use the all active components optimization criterion (see Chapter 2 in the companion volume).

As mentioned above, this application of MOST is using an iterative approach to optimization. An iterative approach involves conducting more than one, in this case two, separate and sequential optimization trials. The research plan calls for us to proceed as follows: Use the first experiment to determine which of the five candidate components described previously have an empirically detectable effect. Any components that do not have an empirically detectable effect are then revised, with the objective of improving their effectiveness. Next, conduct a second optimization trial to evaluate the new set of five components, made up of the components found to be acceptable in the first optimization trial plus the newly revised components. After this second experiment, construct the optimized itMatters intervention using the all active components optimization criterion; in other words, the optimized intervention will consist of all the components that had empirically detectable effects. Finally, proceed to the evaluation phase of MOST and confirm by means of an RCT that the optimized intervention has a statistically significant and clinically meaningful effect.

At the time of this writing, the first optimization trial has been completed, and the second is in the field. Below we describe the general strategy we used for identifying which components require revision and for revising those components in preparation for the second experiment.

### *3.2 Criteria for Determining Whether a Component Has an Empirically Detectable Effect*

Whether each component has an empirically detectable effect will be established in the optimization trial, described below. To our knowledge there are no currently established standards of what constitutes an effective intervention component. We specified a priori that a component will be deemed effective if the results of the optimization trial indicate that it achieves a main effect of $d \geq 0.15$ in the anticipated direction. This is what we consider the minimum clinically significant effect size for a component, and it reflects the notion that in an efficient intervention, every component should have an effect that is at least small by Cohen's rule of thumb (Cohen, 1988). We will also examine interactions between components, though based on the conceptual model, we do not anticipate any large interactions.

We recognize that if there are interactions between components, the combined effect of the components will be different from what would be expected based on the main effects. In particular, if any interactions are primarily antagonistic, this combined effect will be less than what would be expected based on the main effects. Nevertheless, if we are able to arrive at a set of five components that achieve the stated minimum effect size, we expect that the resulting intervention package will achieve an effect size in the $d = 0.35$–$0.5$ range. This would exceed the effects of existing interventions aimed at alcohol use (Scott-Sheldon et al., 2016; Tanner-Smith & Lipsey, 2015) and condom use (Scott-Sheldon et al., 2011).

More about how decision-making can be carried out based on the results of a factorial experiment can be found in Chapter 7 in the companion volume.

### 3.3 Design of the Optimization Trials

As noted above, in this application of MOST, the purpose of the optimization trials is to determine which of the candidate components achieve a main effect of $d \geq 0.15$. The resource management principle (see Chapter 1 in the companion volume) states that the most appropriate experimental design for the optimization trial is one that addresses the key research questions while making the best use of the resources available.

A factorial design was selected for the optimization trials for three reasons. First, a factorial experiment provides the necessary scientific information because it separates component effects, enabling estimation of the main effect of each candidate component (five in the current study). Second, the factorial experiment is the only design that will enable us to examine interactions between components. For example, the results of the factorial experiment will address the question of whether, contrary to our conceptual model, the effect of the expectancies component varies depending on whether a participant is provided with the self-efficacy component. Third, a factorial experiment is a highly efficient way to examine multiple intervention components. To achieve the same statistical power for tests of component effects, a factorial experiment requires substantially fewer participants than alternative approaches, such as conducting individual experiments on each component (Collins, Dziak, & Li, 2009). (For more about factorial experiments, see Chapters 3, 4, 5, and 6 in the companion volume.)

Each of the two factorial experiments to be conducted in the optimization phase uses the same experimental design. There are five factors—a factor corresponding to each component except the information component. Each factor has two levels: no, in which the component is not provided to the participant, and yes, in which the component is provided. A factorial experiment including five two-level factors requires $2^5 = 32$ experimental conditions. Table 1 shows the names assigned to each factor and the 32 conditions in this experiment. Note that all of the participants receive the information component. For example, a participant randomly assigned to experimental condition #8 receives, in addition to the information component, the injunctive norms (*INORM* = yes), perceived benefits (*BENEFITS* = yes), and self-efficacy candidate components (*SELFEFF* = yes). By contrast, a participant randomized to experimental condition #32 receives all of the components.

We considered conducting a $2^{5-1}$ fractional factorial design (see Chapter 5 in the companion volume), which would have cut the number of experimental conditions in half, to 16. This would have meant that, as in all incomplete factorial designs, there would have been aliasing (combining) of effects. In this case, each main effect would have been aliased with a four-way interaction, and each two-way interaction would have been aliased with a three-way interaction. Aliasing can be an acceptable

**Table 1** Experimental conditions in factorial design

| Experimental Condition Number | | FACTORS | | | | |
|---|---|---|---|---|---|---|
| | Information component | *EXP* | *DNORM* | *INORM* | *BENEFITS* | *SELFEFF* |
| 1 | Yes | No | No | No | No | No |
| 2 | Yes | No | No | No | No | Yes |
| 3 | Yes | No | No | No | Yes | No |
| 4 | Yes | No | No | No | Yes | Yes |
| 5 | Yes | No | No | Yes | No | No |
| 6 | Yes | No | No | Yes | No | Yes |
| 7 | Yes | No | No | Yes | Yes | No |
| 8 | Yes | No | No | Yes | Yes | Yes |
| 9 | Yes | No | Yes | No | No | No |
| 10 | Yes | No | Yes | No | No | Yes |
| 11 | Yes | No | Yes | No | Yes | No |
| 12 | Yes | No | Yes | No | Yes | Yes |
| 13 | Yes | No | Yes | Yes | No | No |
| 14 | Yes | No | Yes | Yes | No | Yes |
| 15 | Yes | No | Yes | Yes | Yes | No |
| 16 | Yes | No | Yes | Yes | Yes | Yes |
| 17 | Yes | Yes | No | No | No | No |
| 18 | Yes | Yes | No | No | No | Yes |
| 19 | Yes | Yes | No | No | Yes | No |
| 20 | Yes | Yes | No | No | Yes | Yes |
| 21 | Yes | Yes | No | Yes | No | No |
| 22 | Yes | Yes | No | Yes | No | Yes |
| 23 | Yes | Yes | No | Yes | Yes | No |
| 24 | Yes | Yes | No | Yes | Yes | Yes |
| 25 | Yes | Yes | Yes | No | No | No |
| 26 | Yes | Yes | Yes | No | No | Yes |
| 27 | Yes | Yes | Yes | No | Yes | No |
| 28 | Yes | Yes | Yes | No | Yes | Yes |
| 29 | Yes | Yes | Yes | Yes | No | No |
| 30 | Yes | Yes | Yes | Yes | No | Yes |
| 31 | Yes | Yes | Yes | Yes | Yes | No |
| 32 | Yes | Yes | Yes | Yes | Yes | Yes |

price to pay for greatly increased efficiency (for example, see (Piper et al., 2016)). However, ultimately we decided that in this case, the increase in efficiency would not be great enough to compensate for aliasing. Because all of the candidate components were to be delivered online, the additional resources required to conduct 32 as compared to 16 experimental conditions would have been minimal and, in our view, did not justify the use of a fractional factorial design.

## *3.4 Subjects and Measures*

### 3.4.1 Subjects

Subjects for both optimization trials were freshmen students at several 4-year, coeducational, public universities in the United States. The universities varied in characteristics such as size, location, and ethnic composition, providing a diverse sample.

### 3.4.2 Outcome Measures

The outcome measures for the optimization trials are drawn directly from the conceptual model. As shown in Fig. 1, each component targeted a proximal mediator—expectancies that alcohol is not needed before or during sex, accurate perceptions of how many people use alcohol before or during sex, accurate perceptions of acceptability of using alcohol before or during sex, perceived benefits of using PBS related to alcohol and sex behaviors, and self-efficacy to use PBS related to alcohol and sex behaviors. Measures of these mediators were the outcomes used for making decisions about whether a particular component needs revision. We used proximal mediators as outcomes, instead of the proximal behavioral outcomes of sexual risk behavior in the first experiment, because the proximal mediators could be measured sooner. This helped provide enough time for us to analyze the data, determine which components are working, and make the necessary revisions before conducting the subsequent experiment. We plan to use proximal mediators as outcomes for the second experiment as well as to allow us the time to prepare the itMatters-optimized intervention package for an evaluation by means of an RCT within 1 year.

Our conceptual model justifies this approach. According to the conceptual model, the proximal mediators ultimately affect alcohol-related sexual risk behaviors, which in turn are hypothesized to affect STI incidence. Thus if each component has an effect on its target mediator, this indicates that the optimized intervention package can be expected to have the desired effect on the proximal behavioral outcomes (i.e., alcohol use, use of PBS), the distal behavioral outcome (i.e., alcohol-related sexual risk behaviors), and the distal biological outcome, STIs. As will be discussed below, for the RCT to be conducted in the evaluation phase of MOST, a measure of alcohol-related sexual risk behavior will be used as the primary outcome, and alcohol use and use of PBS will be secondary outcomes.

### *3.5 Revision of Components*

As noted above, this is an ongoing study, with the first of two optimization trials completed. This section describes very briefly how results from the first experiment were used to identify which components needed revision. A regression approach to ANOVA was used to determine which intervention components were satisfactory (i.e., achieved an effect of $d \geq 0.15$) or needed revision (i.e., achieved an effect of $d \leq 0.15$). Preliminary analyses suggest that only the descriptive and injunctive norms components were satisfactory; the remaining three components required revisions. We made some initial revisions based on feedback from student focus groups. We then asked several outside experts to give us a fresh perspective on the revised components. We specifically asked them to identify content that was missing and/or unclear. We revised the components based on their feedback. These components will be evaluated in a second factorial experiment.

### *3.6 Secondary Analysis of Data from the Optimization Trials*

Above we reviewed a number of variables that could be moderators, including gender, race/ethnicity, other individual-level variables, and certain environmental variables. Secondary analyses will examine whether any of these variables moderate the effects of any of the five candidate components. We consider any analyses involving moderating effects to be exploratory and acknowledge that we may not have power to detect moderation effects. However, we expect these analyses to be helpful in generating hypotheses that can be evaluated in subsequent studies that will be powered for that purpose.

## 4 Evaluating itMatters

After the two rounds of optimization trials, we will know which of the candidate components achieved the desired effectiveness on the proximal mediators and will be included in the optimized intervention. The next step will be to evaluate whether the optimized intervention is more effective than a suitable control using a two-arm RCT. The primary outcome for this phase will be the proximal behavioral outcome, alcohol-related sexual risk behaviors. This is the primary outcome specified in the conceptual model, but measuring this outcome requires following students for a longer period of time. We will use the necessary time to measure this outcome in the RCT. If shown to be effective, the optimized intervention will then be released and made available to other universities interested in reducing alcohol-related sexual behaviors and ultimately STIs among college students.

## 5 Discussion

### *5.1 The Conceptual Model*

The first objective of this chapter is to describe the conceptual model for itMatters, an online STI prevention intervention among college students. The development of a conceptual model is a critical part of the preparation phase of MOST. In order to create the conceptual model (Fig. 1), we drew heavily on theory and relevant literature on alcohol use and sexual risk behaviors separately and laboratory studies and the few interventions that have specifically targeted the intersection of alcohol and sex.

The conceptual model is critical in MOST for several reasons. First, during intervention development, the conceptual model has served as a powerful reminder to the research team that it is essential to retain focus on the *intersection* of alcohol and sex, rather than to develop an intervention that is a disjointed amalgam of interventions focused separately on alcohol and sexual behaviors. Second, the proximal mediating variables (i.e., expectancies, descriptive norms, injunctive norms, perceived benefits, and self-efficacy) were clearly identified in the conceptual model as the intervention targets, which guided the content of the components. Third, as discussed above, the conceptual model pointed the way to selection of short-term outcomes for making decisions about the effectiveness of a given component.

Development of a conceptual model can itself be an iterative process. During the course of this project, we have revisited the conceptual model (and the literature) numerous times as new literature emerged and as we refined our understanding of the mechanisms by which alcohol use influences sexual risk behaviors. The research team drafted more than 20 versions of the conceptual model, stopping only when we felt it accurately represented the current empirical literature, scientific theory, and our own ideas about mediating pathways by which proximal cognitive factors influence behavior and ultimately STIs. Figure 1 represents our current thinking.

### *5.2 The Iterative Approach to Optimization*

The second objective of this chapter is to describe the iterative approach to optimization used in the current study. Using sequential optimization trials in an iterative fashion provides an opportunity to improve the effectiveness of individual candidate components before making final decisions about whether or not to include them in the optimized intervention. In the current study, we are conducting two optimization trials, but more than two could be used if resources permit. To conduct two or more optimization trials within a single optimization phase of MOST, it is necessary to have access to enough subjects and sufficient time to conduct multiple experiments.

Because we are conducting this study in university settings, we have a new set of freshmen every year, so we have access to sufficient subjects. Using measures of mediators as short-term outcomes afforded us enough time to conduct two optimization trials in 2 years. However, when mediators are used as short-term outcomes, the test of effectiveness is less definitive than it would be if the outcome of ultimate interest were used. In this case it is particularly important to confirm the effectiveness of the optimized intervention by means of an RCT using the outcome of ultimate interest.

In this application of MOST, we used the all active components optimization criterion, which means we were primarily interested in achieving effectiveness and efficiency. As discussed in the companion volume, economy and scalability may also be important in other settings. For example, in this application we could have used the iterative approach to develop the most effective intervention we could obtain that could be completed within some upper limit on time, say 30 min. This might have improved both the economy (expressed in terms of participant time) and scalability of the intervention. Thus the iterative approach can be used with the objective of improving effectiveness, efficiency, economy, or scalability.

The iterative approach may not be feasible in situations where subjects, for example, clinical subjects, must be recruited over a period of time or offered generous compensation for their participation. It also may not be feasible for interventions that take a long time to deliver or where the outcome of interest is far in the future and it is not desirable to use measures of mediators as short-term outcomes. But where resources permit its use, the iterative approach has considerable appeal, because it has the potential to systematically and incrementally strengthen the effect of an intervention before it is evaluated in an RCT. We are hopeful that the use of this approach will enable us to develop an online intervention that approaches the effectiveness of comparable traditional implementer-led interventions, and we believe it could improve the public health impact of many behavioral, biobehavioral, and biomedical interventions.

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