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One view of the next decade of research on behavioral and biobehavioral approaches to cancer prevention and control: intervention optimization

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Abstract

As a new decade begins, we propose that the time is right to reexamine current methods and procedures and look for opportunities to accelerate progress in cancer prevention and control. In this article we offer our view of the next decade of research on behavioral and biobehavioral interventions for cancer prevention and control. We begin by discussing and questioning several implicit conventions. We then briefly introduce an alternative research framework: the multiphase optimization strategy (MOST). MOST, a principled framework for intervention development, optimization, and evaluation, stresses not only intervention effectiveness, but also intervention affordability, scalability, and efficiency. We review some current limitations of MOST along with future directions for methodological work in this area, and suggest some changes in the scientific environment we believe would permit wider adoption of intervention optimization. We propose that wider adoption of intervention optimization would have a positive impact on development and successful implementation of interventions for cancer prevention and control and on intervention science more broadly, including accumulation of a coherent base of knowledge about what works and what does not; establishment of an empirical basis for adaptation of interventions to different settings with different levels and types of resources; and, in the long run, acceleration of progress from Stage 0 to Stage V in the National Institutes of Health Model of Stages of Intervention Development.

Implications

Practice: Intervention optimization methods provide a principled way to adapt interventions to local circumstances and resource availability while maintaining the highest level of effectiveness possible.

Policy: Intervention optimization methods can be used to produce immediately affordable and scalable interventions, and to improve interventions incrementally over time.

Research: Intervention optimization methods may help researchers learn more about what works and what does not work in behavioral and biobehavioral approaches to cancer prevention and control.

Interventions play a critical role in cancer prevention and control. The U.S. National Institutes of Health (NIH) defines an intervention as "a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints." In this article we focus on behavioral and biobehavioral interventions, both of which use strategies intended to alter an individual's behavior. Behavioral interventions use strategies centered in cognition, skills, attitudes, and beliefs, whereas biobehavioral interventions accompany these strategies with medical or pharmaceutical elements. Behavioral and biobehavioral interventions have been developed for application along most points of the cancer continuum. Examples include interventions related to cancer prevention (e.g., Piper et al.[1]), screening (e.g., Wu et al.[2]), treatment (e.g., Coolbrandt et al.[3]), and survivorship (e.g., Krebs et al.[4]).

Although they vary widely in objectives and approaches, behavioral and biobehavioral interventions for cancer prevention and control have one characteristic in common: They are made up of numerous elements, which we will call intervention components. Here we define an intervention component simply as any part of an intervention that can meaningfully be separated out for study [5], including not only parts of the treatment itself, but also any other aspect of the intervention, such as elements aimed at increasing adherence to or engagement with the intervention or maintaining high-quality intervention delivery. For example, Piper et al.[1] described a smoking cessation intervention including the following components: nicotine replacement therapy (NRT) delivered via mini-lozenge during the 3 weeks leading up to the quit date; starting at the quit date, 26 weeks of NRT delivered via a combination of mini-lozenge and nicotine patch; counseling sessions; and automated calls to prompt medication use.

Considerable progress has been made in behavioral and biobehavioral interventions for cancer prevention and control, much of which has been accomplished by applying the classical treatment package approach to

intervention development and evaluation. In this approach a knowledgeable intervention scientist or, more likely, a team of scientists, identifies an array of components hypothesized to help change behavior; the changed behavior is, in turn, hypothesized to reduce cancer incidence, morbidity, or mortality. The identified components are combined into a package, and after pilot testing as needed, the package is evaluated by comparing its performance against that of a suitable control in a randomized controlled trial (RCT).[1] The purpose of the evaluation is to determine whether the intervention has a statistically detectable and clinically meaningful effect.

In this article we offer our view of the next decade of research on behavioral and biobehavioral interventions for cancer prevention and control. While acknowledging the massive contribution that the classical treatment package approach has made to intervention science in the cancer prevention and control field and beyond, we suggest that entering this new decade inspires re-examination of current approaches to research with a fresh perspective. We begin by discussing several conventions we see as implicit in the classical treatment package approach and how questioning them may reveal opportunities to accelerate progress. We then briefly introduce an alternative to the classical approach called the multiphase optimization strategy (MOST), a principled framework for intervention optimization. We discuss how wider adoption of intervention optimization might have a positive impact on the future of intervention development for cancer prevention and control and intervention science more broadly; some changes in the scientific environment we believe would permit wider adoption of intervention optimization; current limitations of MOST; and future directions for methodological research in this area.

SOME CONVENTIONS IMPLICIT IN THE CLASSICAL TREATMENT PACKAGE APPROACH

In our view, the classical treatment package approach includes a number of implicit conventions. One is that, provided an intervention's overall effectiveness[2] has been established, it is acceptable for the intervention to contain components that are inactive (i.e., their inclusion does not appreciably improve outcomes) or even counterproductive (i.e., their inclusion makes outcomes worse). Yet inactive and counterproductive components consume valuable and finite resources, such as participant and staff time, with no corresponding benefit. An approach that reduces or eliminates such components could move the field forward in several ways. Elimination of counterproductive components would improve outcomes; elimination of inactive and poorly performing components would avoid wasting participant time, which could lead to better participant engagement; and the resulting interventions would be more efficient and less expensive, thus conserving resources.

A second convention is that research questions about affordability and implementability are considered only after intervention efficacy has been established. However, this compartmentalization means that considerable resources are devoted to establishing the efficacy of interventions that are a long way from being practical, and, in some cases, would be difficult to make practical. This may partly explain why, as NIH has noted, "...behavioral interventions frequently do not move beyond efficacy to effectiveness or implementation..." [6]. If affordability and implementability were considered from the beginning and throughout the intervention development process, this could reduce the time to eventual scale-up and even increase the likelihood that scale-up will be successful.

Another convention is reliance on a single type of experimental design, the RCT, even though it is foundational to science that any one type of experimental design cannot address every scientific question. The traditional RCT is an excellent way to evaluate the performance of an intervention as a package, but it is not well suited to addressing questions about the performance of individual intervention components [7]. Openness to a wider variety of experimental designs could help move cancer prevention and control forward by enabling researchers to address a correspondingly wider variety of scientific questions.

A fourth convention is that data analysis proceeds from a conclusion-priority perspective [5], in which classical hypothesis testing is used as a basis for concluding whether there is sufficient evidence to support the idea that a particular parameter, usually the difference between the population outcome means for the intervention being evaluated and a suitable control, is different from zero. However, this approach is not always helpful when the objective is to decide on a course of action, such as whether a component should be included in an intervention or whether an intervention can be considered sufficiently effective that society might consider supporting its implementation, rather than to draw a statistical conclusion about a parameter. Here it may be more helpful to estimate the probability that an intervention component or treatment package will have a desirable effect.

The final convention we note is the expectation that once an intervention has been developed, it remains largely unchanged indefinitely. This runs counter to the approach taken to development of nearly every other product in modern society, such

[1] It can be argued that it would be appropriate to refer to any randomized experiment as a randomized controlled trial. However, in the clinical trials literature the label RCT has, by convention, been reserved for one type of experimental design, in which the objective is direct comparison of the means of a limited number (usually two or three) of experimental conditions or "arms." To avoid confusion, we will adhere to this convention in this article.

[2] In this article we use the term efficacy when referring to work clearly fitting into Stages I, II, or III of the NIH Model of Stages of Intervention Development, and the term effectiveness everywhere else.

as automobiles, medications, foods, computers, smart phones, software, and many others. These are all continually and systematically studied and revised with the objective of improving them and keeping them responsive to modern trends.

We propose that now is the time to consider whether these conventions and others can be questioned, and possibly discarded or replaced, to arrive at an alternative to the classical treatment package approach with the potential to make greater strides in cancer prevention and control over the coming decade. In the next section we describe such an alternative.

BRIEF INTRODUCTION TO THE MULTIPHASE OPTIMIZATION STRATEGY (MOST)

MOST [5, 8–10] is an emerging framework for empirical intervention development that integrates ideas from behavioral science, engineering, and health economics and is now expanding to integrate ideas from decision science and Bayesian statistics. MOST has been used in a number of research projects in cancer and related fields. The smoking cessation area has made particularly extensive use of intervention optimization methods [1, 11–19]. Other examples include research in cancer survivorship [20] and the cancer-related field of overweight [21]. There are many additional examples in a wide variety of other areas of public health and education.

MOST calls for empirical intervention development to proceed (a) in phases, with a phase devoted to principled optimization of the intervention prior to its evaluation in an RCT, and (b) in an iterative and discovery-driven manner, so as to make the best use of research resources in the short run and effect continual improvement in the long run. The purpose of optimization is to arrive at an intervention that achieves intervention *EASE* by strategically balancing *E*ffectiveness against *A*ffordability (extent to which the intervention is deliverable within budget, and offers a good value), *S*calability (extent to which the intervention is implementable in the intended setting with no need for ad hoc modifications), and *E*fficiency (extent to which the intervention is made up solely of active components, i.e., components that, when included, improve outcomes). This section provides an extremely brief introduction to MOST; readers who wish to learn more are referred to Collins [7] and Collins and Kugler [8].

MOST comprises three phases: preparation, optimization, and evaluation. In the preparation phase, the investigator lays the groundwork for optimization. A critical step is developing or revising a conceptual model that provides a detailed description of the process to be intervened on, including the chain of malleable causal factors leading up to the outcome(s), and specifies the components of the intervention and which individual causal factors each component targets. Any pilot testing is done in this phase. It is advisable, although not strictly necessary, to identify the optimization objective in this phase (called the optimization criterion in previous literature on MOST). The optimization objective explicitly defines what is meant by *EASE* in a particular application of MOST. Optimization objectives may feature constraints on resources. Suppose an investigator has determined that a health care system is willing to pay up to, say, $500 per person to implement a smoking cessation intervention. In this case $500 is a constraint, and the investigator seeks to achieve intervention *EASE* by identifying the set of components and component levels that provides the best expected outcome achievable within this constraint on implementation cost. In other settings there may be constraints on resources such as staff time available or tolerable participant burden. However, an optimization objective does not necessarily include explicit constraints. For example, an investigator may wish to identify the most cost-effective intervention, or may simply wish to eliminate any inactive components to arrive at an efficient intervention without any explicit consideration of cost.

The next phase involves optimization of the intervention. Here one or more optimization trials are conducted to examine the performance of intervention components that are candidates for inclusion in the optimized intervention and, where possible, whether these candidate components interact. There are many optimization trial designs from which to choose, including factorial and fractional factorial designs [22–25], the sequential multiple assignment randomized trial (SMART [26]), the micro-randomized trial (MRT [27]), and the system identification experiment [28]. The investigator selects an optimization trial design based on the resource management principle, which states the imperative of moving intervention science forward as quickly as possible by selecting the most efficient experimental design that appropriately addresses the scientific questions at hand. The scientific questions, and therefore the choice of experimental design, are partially determined by whether the intervention to be optimized is fixed (all participants are to receive the same intervention dose and content) or adaptive (intervention dose or content are strategically varied in response to measured characteristics, environment, and/or progress of the individual). Factorial and fractional factorial designs are used for optimization of fixed interventions, and, under some circumstances, adaptive interventions. SMARTs, MRTs, and system identification experiments are used for optimization of adaptive interventions. The optimization phase may be followed by the evaluation phase, in which the performance of the optimized intervention as a package is assessed in an RCT.

For example, the smoking cessation intervention mentioned above and described in Piper et al. [1] was constructed by conducting two optimization trials, one using a factorial design [14] and one using a fractional factorial design [15]. Out of the 11 components examined, four were selected for inclusion in the optimized intervention. Among the components that did not perform well enough to be included in the optimized intervention were use of nicotine patches prior to the quit date (the intervention includes use of nicotine patches starting at the quit date) and counseling concerning medication adherence during the cessation period.

Throughout MOST, decisions must be made, such as deciding on the composition of the optimized intervention, based on the results of the optimization trial along with information on resource utilization (e.g., cost of implementation; time required of participants). The decisions about which components or component levels merit inclusion in the optimized intervention can be complex, particularly when the need for affordability and scalability constrains decision-making such that costs and benefits have to be carefully adjudicated, or when there are multiple stakeholders involved in decision-making.

Decision-making is inherent to the iterative and discovery-driven nature of MOST. Any results obtained in any of the phases of MOST directly inform immediate next steps. For example, once the optimization phase has been completed, the conclusions based on the data and next steps might be any of the following: (a) The optimized intervention is likely to be satisfactory, and an RCT is needed to confirm the effectiveness of the treatment package before the intervention is scaled up; (b) The evidence from the optimization trial is so strong that an RCT would be a redundant waste of resources, and the intervention can go to scale immediately; or (c) The evidence from the optimization trial suggests that not enough components are having an effect on the outcome to make up an effective intervention, so an RCT would be a waste of resources for quite different reasons from those operating in (b) (and moreover would probably be unethical). In this last case investigators would likely go back to the drawing board, so to speak, by returning to the preparation phase, reconsidering the conceptual model, and identifying new candidate components. Any components that performed adequately in the optimization trial can be retained. In the section "Current limitations of MOST and future directions" we briefly discuss our current work on development of Bayesian methods to assist investigators with decision-making in MOST.

A FUTURE IN WHICH INTERVENTION OPTIMIZATION IS STANDARD OPERATING PROCEDURE: RECONSIDERING IMPLICIT CONVENTIONS

In this section we envision a future in which intervention optimization is standard operating procedure, enabling the conventions associated with the classical treatment package approach that were reviewed above to be reconsidered as described below.

First, in this future there is no longer a need to tolerate inert or counterproductive components, because eliminating them is an essential part of intervention optimization. As a result, interventions are more efficient, less wasteful, and less burdensome for staff and participants.

Second, a high priority is placed on arriving at interventions that are not only effective, but also immediately affordable and scalable. To accomplish this, resource constraints expected to affect how an intervention is implemented in its intended setting, such as limitations on staff time or funds to support implementation, are established at the very outset of intervention development. Interventions are then optimized to be as effective or cost-effective as is achievable within these resource constraints. Research can readily be designed so as to provide sufficient information for intervention scientists to be confident they are developing a package that has the highest potential to be deemed effective, affordable, efficient and implementable.

Third, experimental designs are selected according to the research objectives at hand. During intervention optimization, investigators select optimization trial designs that are appropriate and efficient for testing the efficacy of individual intervention components and examining whether the presence or absence of certain components have an impact on the efficacy of others. As was mentioned above, typically these designs are drawn from outside the family of RCTs. During the evaluation phase, usually an RCT is used to evaluate an optimized intervention package.

Fourth, where useful and appropriate investigators may conduct research primarily from a decision-priority perspective, as opposed to the more common conclusion-priority perspective. Here the emphasis is on using empirical evidence to determine next steps, for example deciding what the composition of the optimized intervention should be, or whether or not to proceed to an RCT after the optimization trial. When working from the decision-priority perspective investigators may rely on Bayesian statistics, which are a natural fit with this perspective, and indeed for many years have been recognized as an important tool in making decisions based on complex empirical data (e.g., Spiegelhalter et al. [29]).

Fifth, rather than remaining constant, interventions are optimized repeatedly and iteratively—in other words, continually—to make them more effective, affordable, scalable, and efficient by adding, removing, replacing, or updating components. Because continual optimization of interventions is a norm, practitioners expect that each version of an intervention will be replaced by a new one

periodically, much as is routinely expected of software and other products. In some cases, successive or alternative versions of interventions are even assigned numbers to distinguish among them and to reflect incremental improvements over time in the intervention's responsiveness to public health needs and its overall public health impact. Continual optimization is consistent with NIH's assertion that "... intervention development is not complete until an intervention reaches its maximum level of potency *and* is implementable with a maximum number of individuals in the population for which it was developed" [6].

For example, consider a smoking cessation intervention that has been optimized to deliver the greatest effectiveness obtainable within a cost of $200 per participant. Subsequent optimization trials (conducted alongside widespread implementation of the intervention) could investigate new components with the objective of producing an improved intervention that is (a) less expensive but of comparable effectiveness; (b) of comparable effectiveness and with the same upper limit on cost, but requiring less participant time; (c) implementable at the same cost, but with increased effectiveness, perhaps here testing candidate replacements for components found to be relatively weak in prior optimization trials, or examining innovative components representing translations of the latest basic science findings; or achieving other objectives. Under some circumstances a hybrid evaluation–optimization trial [30] can be used to enable simultaneous evaluation of a newly optimized intervention and empirical testing of new components. If the current optimized intervention has been deemed effective, it is usually not necessary to withhold it from participants in an optimization trial; instead, it may be possible to provide the intervention to all participants in addition to their randomly assigned treatment.

IMPROVING CANCER PREVENTION AND CONTROL BY ADOPTING INTERVENTION OPTIMIZATION AS STANDARD PRACTICE

We suggest that widespread adoption of intervention optimization as standard practice could shape the future of cancer prevention and control in a variety of positive ways. In this section we highlight several of these ways.

First, it is likely that as an increasing number of optimization trials are reported in the scientific literature, a coherent and growing body of knowledge about what works and what does not, and how intervention components may interact, will become established. A movement toward what NIH has called "a cumulative, progressive field" [6] is already emerging in smoking cessation, an area in which, as mentioned above, there have been numerous applications of optimization methods. This body of knowledge would be built upon as each new intervention is launched and each existing intervention is improved. For example, once the efficacy of a particular component has been satisfactorily established, it may be possible to include it in certain interventions with no further testing. Again, this requires decision-making based on empirical data to determine when efficacy has been "satisfactorily established."

Second, optimization trial results could help inform adaptation of interventions to individual settings (as distinct from optimization of adaptive interventions, which, as discussed briefly above, adapt to the characteristics and progress of individual participants). Consider a hospital-based intervention to encourage and aid smoking cessation in smokers who come into the emergency department (e.g., Bernstein et al.[12]). Suppose Setting A is a private hospital with a well-staffed emergency department and a relatively high level of resources, and Setting B is a public hospital with fewer emergency department staff and a lower level of resources. Further suppose researchers aim to identify the most effective set of components that can be implemented within a set of constraints. These two settings are likely to have different constraints. Setting A may be able to afford to support a more expensive intervention than Setting B; for example, staffing levels may permit more time for delivering the intervention to individual participants in Setting A than Setting B. Thus, it stands to reason that an intervention optimized for Setting A may not be implementable in Setting B; conversely, an intervention optimized for Setting B may be suboptimal for Setting A if Setting A's resources would support additional components that would improve effectiveness.

An ideal approach would be to increase Setting B's resources, but if this is not possible, the best can be made of an unfortunate situation by using optimization methods to develop interventions that deliver the highest degree of effectiveness achievable in each setting. The results of a single optimization trial can be used to arrive at multiple optimized interventions, in this case one optimized for Setting A and a (likely) different one optimized for Setting B. This is not merely a matter of optimizing for Setting A and removing a few components; it is straightforward to demonstrate (see Collins [5], p. 256) that the intervention optimized for Setting B does not necessarily comprise a subset of the components included in the one optimized for Setting A. This approach requires assuming that the results of the optimization trial can reasonably be expected to generalize across both settings, just as it would be necessary to assume that the results of an RCT generalize similarly if an intervention developed using the treatment package approach were under consideration for implementation in both settings.

It should be noted that even if the intervention optimized for Setting A is highly effective at

increasing smoking cessation among emergency department patients, there is no guarantee that the expected increase in smoking cessation delivered by the intervention optimized for Setting B will be sufficient to justify its implementation, particularly if the constraints in Setting B are severe. The results of the optimization trial can be used to model expected effectiveness and inform the decision about whether the next step should be implementation of the optimized intervention, an RCT that will inform the decision about whether to implement the intervention, or another optimization trial to examine the performance of new components.

Third, MOST has the potential to expedite long-run progress from Stage 0 (basic science) to Stage V (implementation and dissemination) in the NIH Stage Model for Behavioral Intervention Development [6]. Imagine conducting a series of optimization trials as Stage II and Stage III research. The Stage II optimization trial could be used to identify which of a set of candidate components is working and which are not under controlled research settings, as well as to obtain preliminary data on cost and obtain a sense of which components are likely to work well enough to justify their cost. Consistent with the iterative nature of MOST, if the results of the optimization trial suggest not enough components are working satisfactorily, the next step would probably be another Stage II optimization trial. This would be disappointing, but perhaps not as disappointing as nonsignificant results in an RCT, because unlike an RCT the optimization trial would show which components worked and which did not. This helps illuminate the way forward; any components that worked in the previous trial can be retained, and any that did not can be revised or replaced with new ones.

At the conclusion of a Stage II trial, if enough components have been found to work, the research could proceed to a Stage III optimization trial. Here the focus could be replication of the results of Stage II in a controlled community setting, possibly testing some additional components aimed at encouraging participant engagement; or the focus could be on optimization of program implementation, with examination of components related to quality and fidelity of delivery. The culmination of the Stage III research could be optimization of the intervention, based on the results of the Stage III optimization trial and any data collected on cost. If Stage IV is entered with an intervention that has been engineered to be the most effective or cost-effective intervention achievable within the identified constraints, this increases the probability that it will be demonstrated both effective and immediately scalable. An optimization trial conducted as a Stage V study would be concerned with optimization of implementation strategy, and therefore would involve experimental manipulation of implementation strategy components. This may require cluster randomization, which is feasible in many optimization trials [24, 25].

CURRENT LIMITATIONS OF MOST AND FUTURE DIRECTIONS

MOST is a relatively new approach, and much methodological work remains to be done. There are a number of areas in which MOST is currently limited, some of which are active areas of inquiry.

First, to date MOST has not been applied much to optimization of social-structural interventions, such as clean air laws to restrict where people can smoke. Here the unit of analysis may be communities, school districts, towns, counties, and so on, rather than the individual, and the outcomes may be drawn from public records rather than direct measurement. It may be possible to apply MOST in this context by conducting an optimization trial using econometric time series data as outcomes; to our knowledge this has not yet been tried.

Second, as we have mentioned, MOST offers the possibility of including multiple stakeholders in planning and decision-making. Depending on the intervention and the circumstances, the set of stakeholders may include, for example, scientific team members, community representatives, potential participants/patients, providers, and payers. However, to our knowledge such a broad set of stakeholders has not been involved in intervention optimization. One reason may be that it is often unclear not only who the stakeholders are, but also how to identify them. Another reason may be that approaches for obtaining information from stakeholders and managing the input of multiple stakeholders in decision-making have not yet been developed. More research in this area is needed.

A third area of MOST that is currently underdeveloped is how to make decisions about the composition of the optimized intervention based on the results of the optimization trial and any other desired information, such as cost. One strategy for decision-making based on optimization trial results has been outlined [7, 31]. However, this approach is severely limited because it is based on classical hypothesis testing and pertains only to cases in which there is a single outcome and a defined upper limit on resource expenditure (e.g., an implementation cost of $200 per participant).

We see great promise in the advancement of alternative decision-making strategies for intervention optimization that make use of the benefits of the Bayesian paradigm [32–34] and multicriteria decision analysis [35, 36]. Such strategies can flexibly incorporate data from an optimization trial that includes multiple empirical outcomes and can also incorporate multiple resource constraints. In these

strategies, each component's overall contribution to efficacy (including the component's ability to enhance or dampen the efficacy of other components) is expressed in the "joint" (or multivariate) posterior distribution, representing how knowledge about the efficacy of components is cross-linked through the observed data. When multiple outcomes are of interest, the joint posterior distribution characterizes potential synergies and tradeoffs across outcome domains—for example, when a component (say intensive monitoring of patient-reported symptoms) improves both early detection of adverse events and adherence to chemotherapy but also increases the number of patient visits to the oncologist. The outcomes may be assigned weights that reflect their relative importance in decision-making.

This approach may provide a way to include multiple stakeholders in decisions about the composition of the optimized intervention and quantify their input when different stakeholders value each outcome domain differently. Patients, for example, may place more weight on a particular set of symptoms, whereas providers may place more weight on treatment adherence, and the healthcare system may focus on the use of a set of constrained resources. Multicriteria decision analysis can use information obtained during the optimization phase to help identify the combination of components likely to offer the greatest value from the point of view of each stakeholder. Although different stakeholders may not agree on which combination is optimal, they will at least have a mechanism by which each can understand the perspective of the others. This may make it possible to move forward to identify an intervention that has a mutually agreeable combination of effectiveness, affordability, scalability, and efficiency.

A fourth open area concerns how Bayesian statistics can support the iterative and discovery-driven nature of MOST. Although the literature on MOST to date has presented it as a predominantly linear progression through the preparation, optimization, and evaluation phases, we believe that considerably more progress in intervention science can be made, and better use made of finite research funding, with a more flexible Bayesian approach to the entire process. In Bayesian statistics uncertainty about a treatment component's effect on an outcome is completely captured in the posterior distribution of its effect parameters. The posterior expresses how likely each magnitude of effect size is given (a) the experimental data in front of the analyst and (b) the prior distribution representing what information from other sources has previously obtained about effect magnitude. Notably, prior information can come from prior research or from earlier data collected in the current experiment using a so-called "sequential analysis." Bayesian sequential designs can continually assess the probability of different effect sizes as an optimization or evaluation trial progresses.

The development of Bayesian methods for use in MOST will make it possible for the investigator to decide during the course of the optimization or evaluation trial whether evidence about the effect (which may be a combined effect including multiple outcomes) of a component or treatment package has been "satisfactorily established." Consistent with the resource management principle of MOST (mentioned above), investigators can consider the costs (in money and time) of continuing to enroll subjects and decide, for example, whether the optimization phase should continue, or if this phase can be concluded and an evaluation of the optimal combination of components via an RCT begun. The same principles can apply to the evaluation trial itself, with a decision to stop enrollment once stakeholders decide that enough evidence has been accrued to support implementing the intervention at scale. Indeed, the transition between phases can be "seamless," as is increasingly the case in Phase 2B/3A biomedical trials using Bayesian methods.

In the event that the optimization phase suggests that no combination of components is likely to produce sufficient value from the perspective of the investigators, payers, or other key stakeholders, the investigators can decide to return to the preparation phase, reconsider the conceptual model, and select new components to investigate in the next optimization trial. If the evaluation trial indicates that the optimized intervention is not doing as well as expected, the optimization phase can be reopened—carrying back information learned in the evaluation phase, which can be incorporated in the new study through the prior distribution. Findings of "futility" are no doubt a disappointment, but the compensation is that resources saved from avoiding or shortening a trial can be repurposed into developing intervention components that work better. Greater efficiency in intervention discovery, development, optimization, and evaluation can shorten the time from idea to impact on cancer prevention and control—something all stakeholders should find beneficial.

CHANGES IN THE CANCER PREVENTION AND CONTROL SCIENTIFIC ENVIRONMENT THAT WOULD FACILITATE INTERVENTION OPTIMIZATION

Compared to the classical treatment package approach, MOST is a very different way of conducting intervention science. As a consequence, it is not always a comfortable fit with the current scientific environment. In this section we review some changes in the reward and funding structures that we believe would pave the way for more optimization in cancer prevention and control research.

The reward structure

Based on our own observations, we have identified two aspects of the existing reward structure that

could be reconsidered to encourage intervention optimization.

First, in the current research paradigm intervention scientists are rewarded with publication, grant funding, promotion, tenure, acclaim, and, indeed, a sense of accomplishment and purpose when they establish to the scientific community that the treatment packages they have developed are efficacious. Traditional RCT designs with populations, control interventions, and endpoints chosen to maximize statistical power may serve this end well. This reward structure does not sufficiently recognize the contributions to intervention science that can be made by optimization trials. The optimization trial in MOST is not merely a lead-up to the main event of an RCT, and most emphatically is not a pilot study conducted in preparation for an RCT. Rather, optimization trials are important in their own right because they gather different and equally valuable kinds of scientific information. We propose that the science of cancer prevention and control will move forward faster if, alongside its recognition of the contributions made by RCTs, the professional reward structure explicitly recognizes the distinct contributions that optimization trials can make.

Second, striving to achieve a high degree of intervention efficacy is often incentivized more than balancing efficacy against the reality of practical considerations to achieve scalability and, ultimately, public health impact. The short-term benefits of focusing primarily on efficacy are evident. As mentioned in the previous paragraph, many professional rewards accompany obtaining a significant effect in an RCT. All else being equal, obtaining a significant effect in an RCT is more likely if the effect size attributable to the intervention being evaluated is larger. Moreover, as discussed earlier in this article, by convention currently the presence of inactive components is considered acceptable as long as the intervention as a package shows a significant effect in an RCT. From this perspective, when creating a treatment package for evaluation it is logical, even advisable, to include any and all components that are judged capable of having even a small salutary effect on the outcome, and to defer any consideration of cost except insofar as concerns the research budget. In our experience there appears to be little expectation (at least in the United States) that intervention scientists identify who would be expected to pay for the interventions they develop when they eventually go to scale, even though it could be argued that establishing that there is some entity with some interest in supporting implementation is an essential early step.

It is easy to see how such a reward structure may inadvertently incentivize the development of more efficacious but *less* efficient, affordable, and scalable interventions. However, from the perspective of those who deliver and pay for interventions, whether in an individual or public health setting, a demonstration of even dramatic treatment efficacy may say little about whether the intervention can work in their own setting with its own participants, providers, and resource constraints, and whether it is or could feasibly be made affordable while maintaining sufficient effectiveness to make it worthwhile—in other words, whether it will ever actually be implemented. Even an extremely efficacious intervention will have a net public health impact of zero if it is never implemented successfully. Thus, an emphasis on efficacy at the expense of practical considerations runs counter to long-term goals in cancer prevention and control, as well as other areas of public health.

Not all intervention research is or should be aimed at developing an implementable intervention. There will always be a role for basic behavioral research aimed primarily at establishing whether a strategy will work under ideal and carefully controlled conditions. One approach would be for funders to require that a clear distinction be maintained between research for the purpose of scientific discovery to inform future intervention development and research intended to develop an intervention that ultimately will be broadly implemented. When the objective is the latter, funders could incentivize the development of efficient optimized interventions that explicitly balance efficacy against affordability and scalability. For example, intervention scientists could be encouraged to identify one or more payers—health care systems, school districts, private foundations, and the like—that express an interest in supporting the implementation of the intervention after it has been developed and evaluated. Then the input of these payers, along with that of other stakeholders who would be likely to implement or participate in the intervention, could be obtained starting at the very beginning of intervention development. This input could help determine, for example, whether there are upper limits on affordability, participant burden, and the like. There could also be recognition and rewards for scientists who develop interventions that are successfully and sustainably implemented.

The funding structure

One way the funding structure could be modified to help facilitate the uptake of intervention optimization methods would be the creation of appropriate NIH mechanisms for funding optimization trials. The R34 mechanism is usually a good fit for the preparation phase of MOST, and the R01 is a good fit for the evaluation phase of MOST, which consists primarily of an RCT. However, neither mechanism is a good fit for an optimization trial. As mentioned above, optimization trials are not pilot studies, so their resource requirements typically exceed what can be provided by the R34 mechanism. Most funding of optimization trials to date has been

via the R01 mechanism, but anecdotal evidence (and the personal experience of one of the authors of this article) suggest that one obstacle in review has been the prevailing (but happily not universal) expectation that whatever else may be accomplished in an R01 in the intervention science field, it must include an RCT. Among the reasons not to propose an RCT along with an optimization trial, one of which is discussed below, is the practical limitation that the five-year time span of an R01 may be too short to accomplish both. There is even more difficulty in determining how to obtain funding for an optimization trial devoted to examination of components for the purpose of incremental improvement of an existing intervention. In our view this kind of work is essential for continual improvement of interventions, but we know of no funding announcements calling for such research.

If NIH wishes to facilitate the uptake of intervention optimization, it could issue funding announcements calling specifically for optimization trials, both for development of new interventions and improvement of existing interventions, and establish new funding mechanisms to support the conduct of optimization trials. NIH might also consider determining the ideal balance of its behavioral intervention science portfolio with respect to research based on the classical treatment package approach and research based on optimization.

Even more important than the lack of appropriate funding mechanisms are certain prevailing expectations about how research should be proposed and conducted. These expectations discourage the iterative and discovery-driven approach that is necessary for intervention optimization and ultimately for moving interventions through the NIH Stages of Intervention Development to successful implementation and public health impact. For example, consider an investigator who wishes to apply for R01 funding to support intervention optimization. The investigator faces a dilemma about whether to propose solely an optimization trial, or an optimization trial followed by an RCT. On the one hand, the investigator knows that review panels tend to expect an RCT and therefore may view the application favorably if an RCT is included, and in any case the investigator is likely to want to conduct an RCT once a suitable optimized intervention has been identified. On the other hand, a review panel may, not unreasonably, assess that a subsequent RCT specific aim is contingent on the success of the optimization specific aim, and reduce the impact score of the entire proposal because of perceived risk of failure.

For these reasons the investigator would greatly prefer to propose an iterative and discovery-driven research plan, in which an initial optimization trial would be followed by *either* proceeding to the evaluation phase of MOST *or* remaining in the optimization phase to obtain additional information, with the course of action *to be determined based on the results of the initial optimization trial*. Such a plan is sensible; consistent with both scientific training and the principles of intervention optimization; and likely to advance intervention science rapidly by generating useful knowledge about what does and does not work. Yet a plan of this type is virtually certain to be unacceptable by today's review criteria, which demand a predetermined road map to be followed throughout a funded project, providing little opportunity for discovery-driven decision-making.

It would be possible to make the funding structure more flexible and more consistent with how intervention optimization is ideally conducted, while retaining a reasonable degree of accountability to funders. One approach would be to require applicants to propose the optimization trial along with a limited number of possible next steps, including explicitly and clearly specified criteria for selecting the next step based on the results of the optimization trial. Ideally, these next steps would be guided by formal assessment of the expected net benefit of sampling [37], a concept from decision theory weighing the benefits of improved decision-making likely to be obtained from additional data collection under alternative designs against the resource and time delay costs. The budget could include not only requirements for the optimization trial, but also contingent funding for each of the possible alternatives for the subsequent study. Such an approach would require scientists to submit to peer review a description of an overall approach to obtaining information and criteria for making decisions, but a detailed roadmap only up to the first decision. Then as research proceeds, decisions could be made about what the next steps should be to ensure the most valuable information is obtained—whether to continue with the current experiment or conclude it and start a new one, and if the latter, what scientific information is to be obtained in this new experiment—at critical junctures. The program official could represent NIH as a stakeholder in this decision-making, and a panel of scientists could objectively represent the field in much the same way data safety and monitoring boards operate. Funding priority could be assigned based on the value of the information to be obtained, thereby maximizing the scientific yield of each NIH dollar spent on research.

CONCLUSIONS

In this article we have offered one possible view of the next decade of research on behavioral and biobehavioral approaches to cancer prevention and control. In this future, behavioral and biobehavioral interventions for cancer prevention and control are optimized before they are evaluated; there is an emphasis on achieving intervention *EASE*, a strategic balance of effectiveness, affordability, scalability, and efficiency; and funding is set up so that research

can be conducted as efficiently and economically as possible, in an iterative and discovery-driven fashion. As a result, a coherent body of scientific and practical knowledge is rapidly accumulated about what works and what does not; interventions frequently move past Stage V and on to successfully prevent and control cancer; and continual optimization means that these interventions for cancer prevention and control become incrementally and demonstrably better and better over time.

We are optimistic that this future is within reach. However, getting there will require significant changes in many aspects of intervention science, including how intervention scientists are trained; how they conceptualize, plan, carry out, and evaluate research; which activities and accomplishments are rewarded in a career in intervention science; and how NIH structures and awards funding. To those who find our view of the next decade of research appealing and would like to play a part in making it a reality, we offer the following suggestions:

- Learn more about intervention optimization so that you can readily apply these ideas in your work. A good starting point would be to read Collins [5] (available for free download at many university libraries). Online training on intervention optimization will soon be available.
- When reviewing journal articles and grant proposals, rather than starting from the perspective that an RCT is the primary means of contributing to intervention science, be open to the unique contributions to knowledge that can be made by a well-conducted optimization trial.
- Promote graduate training in intervention optimization at your institution.
- If you are junior faculty, keep in mind that although establishing a career in intervention optimization may appear to be a somewhat more arduous and riskier path, this field is full of opportunities for innovative and exciting work. Seek mentors who can help you strategize to establish a successful and high-visibility career in intervention optimization.
- If you are senior faculty, be mindful and appreciative of the scientific contributions of optimization trials when in a position to evaluate an individual for hiring, promotion, or tenure. Be vocal about encouraging your colleagues to do the same, and be available as a mentor to junior faculty interested in intervention optimization.
- Encourage NIH to restructure its approach to funding research as discussed above, so as to enable a more iterative and discovery-driven approach to scientific inquiry, and thereby facilitate intervention optimization and ensure that more interventions progress through the NIH Stages of Intervention Development to successful and impactful implementation.

Anyone who follows these suggestions will be promoting fundamental changes to behavioral intervention science and may meet with a certain amount of resistance. However, our experience has been that intervention optimization is gradually gaining traction. We look forward to a time when intervention optimization becomes the norm and behavioral interventions begin to fulfill their potential to reduce morbidity and mortality from cancer, contribute to many other areas of public health, and enhance human well-being.

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Conflict of Interest: Dr. Collins, Ms. Strayhorn, and Dr. Vanness declare they have no conflicts of interest.

Informed Consent: This article does not contain any studies with human participants and informed consent was therefore not required.

Welfare of Animals: This article does not contain any studies with animals.

Transparency Statements

Study Registration: This study was not formally registered, because it is not based on collection of empirical data.

Analytic Plan Pre-registration: This study did not pre-register an analytic plan, because it does not involve data analysis.

Data Availability: This study does not involve any data.

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