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Using Decision Analysis for Intervention Value Efficiency to Select Optimized Interventions in the Multiphase Optimization Strategy

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Objective: Optimizing multicomponent behavioral and biobehavioral interventions presents a complex decision problem. To arrive at an intervention that is both effective and readily implementable, it may be necessary to weigh effectiveness against implementability when deciding which components to select for inclusion. Different components may have differential effectiveness on an array of outcome variables. Moreover, different decision-makers will approach this problem with different objectives and preferences. Recent advances in decision-making methodology in the multiphase optimization strategy (MOST) have opened new possibilities for intervention scientists to optimize interventions based on a wide variety of decision-maker preferences, including those that involve multiple outcome variables. In this study, we introduce decision analysis for intervention value efficiency (DAIVE), a decision-making framework for use in MOST that incorporates these new decision-making methods. We apply DAIVE to select optimized interventions based on empirical data from a factorial optimization trial. ***Method:*** We define various sets of hypothetical decision-maker preferences, and we apply DAIVE to identify optimized interventions appropriate to each case. ***Results:*** We demonstrate how DAIVE can be used to make decisions about the composition of optimized interventions and how the choice of optimized intervention can differ according to decision-maker preferences and objectives. ***Conclusions:*** We offer recommendations for intervention scientists who want to apply DAIVE to select optimized interventions based on data from their own factorial optimization trials.

Public Significance Statement
The multiphase optimization strategy (MOST) has been applied across a wide variety of public health contexts (smoking, HIV, cancer, substance misuse, and so on) to advance behavioral and biobehavioral interventions capable of public health impact. Novel decision-making methods for use in MOST open new possibilities for intervention optimization, including optimization based on the strategic consideration of (a) effectiveness on multiple valued outcome variables and/or (b) opportunity costs. We highlight these new possibilities using an empirical example from HIV care.

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Behavioral and biobehavioral interventions often contain multiple intervention components, each hypothesized to contribute in some way to the success of the intervention. For example, an intervention to move individuals along the HIV care continuum could include components like HIV health education; motivational interviewing; skill building to promote treatment adherence skills and habits; peer mentorship; focused support groups; and assistance with accessing the healthcare and social service systems (Gwadz et al., 2017). Selecting components that are effective in producing the desired outcomes is challenging—especially when the goal is to advance an intervention that will be not only effective but also readily implementable. One way to make eventual implementability more likely is to keep the intervention as straightforward to implement and affordable as possible. Intervention scientists can facilitate this by making strategic decisions about intervention components and including only those for which the effect, exerted directly or through interaction with other components, is expected to justify the cost in money, time, or another limited resource.

There can be various forms of this sort of strategic decision-making. In this article, we focus on decision-making based on empirical information about intervention components. Notably, when promising intervention components are combined as a package a priori and then evaluated together as a complete package, for example, via a two-arm randomized control trial (RCT; a "treatment package strategy"; Kazdin, 1979), the effects of the components that make up that package are not estimated empirically. As a result, the evaluation of a complete treatment package cannot directly inform modifications to the interventions for better affordability, scalability, or efficiency in resource use. There have been calls in a variety of disciplines for the use of alternative approaches that enable more nuanced decision-making about intervention components (e.g., Collins et al., 2005; Kazdin, 2000; West & Aiken, 1997), with particular emphasis on research designs that employ randomization in empirically estimating component effects, such that effect estimates can then be weighed against cost(s), for example, via linear programming or other methods from operations research (e.g., Yates, 1980).

The general category of multiple-arm comparative experiments (Collins et al., 2009, 2014) offers one approach to empirically estimating component effects. In the prototypical multiple-arm comparative experiment, there is one experimental arm corresponding to each individual component and one more arm for a suitable control condition. A simple effect for each component is typically estimated by comparing the mean outcome for the component arm to the mean outcome for the control arm. Alternatively, when the effectiveness of a complete treatment package has already been established, arms may be selected differently. For example, in a dismantling treatment design (Kazdin, 1979; Nezu & Perri, 1989) one arm usually receives the full treatment package while others receive versions of the package that have been "dismantled," with one or more components removed. Comparing mean outcomes for arms in a dismantling treatment design enables investigation of whether there appears to be a significant difference between the full package and the dismantled version(s).

In this article, we use a different approach to assessing the contributions of intervention components. Specifically, we take an intervention optimization perspective, defined in terms of the multiphase optimization strategy (MOST; Collins, 2018). In MOST, intervention optimization is a process of identifying, from a set of candidate intervention components, the combination that is best expected to demonstrate intervention *EASE* in a subsequent confirmatory study because it strategically balances *Effectiveness* with *Affordability* (the extent to which the intervention is deliverable within a specified budget), *Scalability* (the extent to which the intervention is implementable without modification in a given setting), and/or *Efficiency* (the extent to which the intervention contains only components that are sufficiently active in producing the desired effects). MOST consists of multiple phases of research, and identifying the optimized intervention (composed of some combination of candidate components) is done in an optimization phase that precedes a subsequent evaluation phase. Key challenges of the optimization phase are (a) to assess, using a rigorous optimization trial, the individual and combined performance of components and (b) to make decisions about which package of components to advance further (i.e., for evaluation, frequently in an RCT).

One popular optimization trial design is the 2^k factorial experiment (e.g., Piper et al., 2016; Spring et al., 2020; Wyrick et al., 2014), also widely used in agriculture and engineering (Montgomery, 2020). In a full 2^k factorial optimization trial, candidate intervention components are operationalized as k two-level factors (e.g., with levels "off" vs. "on," indicating presence vs. absence in the package), and there are 2^k experimental conditions, one for each combination of factor levels. Effects for the k factors are estimated and interpreted differently than in a multiple-arm comparative experiment; a main effect for a given factor (vs. a simple effect) is estimated by comparing the mean outcome for conditions with one level of that factor to the mean outcome for conditions with the other level of that factor, collapsing across the levels of the remaining factors (Montgomery, 2020). The main effect, therefore, quantifies the average effect of the factor overall levels of the remaining factors. A two-way interaction indicates that the main effect for one factor differs depending on the level of a second factor, a three-way interaction indicates that a two-way interaction effect differs depending on the level of a third factor, and so on. In a full 2^k factorial experiment, k main effects on a given outcome can be estimated, as well as $2^k - k - 1$ interaction effects.

However, the great advantage of the 2^k factorial experiment—namely, the wealth of empirical information generated, including both main and interaction effects—also presents challenges for decision-making about the composition of the optimized intervention, since the empirical information about effectiveness has to be consolidated, along with any information about additional *EASE* criteria (*Affordability*, *Scalability*, *Efficiency*), to arrive at an optimized intervention. When there are k factors representing candidate components, there are 2^k alternatives for the optimized intervention (e.g., when $k = 5$, $2^k = 32$ alternative versions of the intervention, each consisting of some combination of components). There is a need for methods to guide decision-making based on the empirical results of a factorial optimization trial (Collins et al., 2021).

Methods for Decision-Making Based on Factorial Optimization Trial Results

The initial approach for decision-making about which components merit inclusion in an optimized intervention in MOST was a component screening approach (Collins, 2018; Collins et al., 2014), which typically relied on hypothesis testing about main and/or interaction effects to inform the screening process. However, recent advances in methods for decision-making in MOST suggest an alternative posterior expected value approach, which makes use of methods from Bayesian decision science (Savage, 1972) and multicriteria decision analysis (MCDA; e.g., Keeney & Raiffa, 1976; Thokala et al., 2016). Notably, the posterior expected value approach does not rely on hypothesis testing or an analogous approach to explicitly considering statistical significance, but rather bases the selection of an optimized intervention on comparisons among the posterior expected values of all alternative interventions under consideration. As described more in the "Method" section, this is consistent with precedents in the decision science literature (e.g., Claxton, 1999). In extensive Monte Carlo simulation (Strayhorn et al., 2023), a posterior expected value approach outperformed a component screening approach, identifying superior optimized interventions on average.

Moreover, a posterior expected value approach to selecting optimized interventions responds to two key limitations of the initial component screening approach (Collins et al., 2021). First, a component screening approach was limited to cases in which costs could be considered in terms of a strict upper limit, usually a limit on affordability. Certainly, component costs can have implications in terms of affordability: that is, when components are selected and combined, the resulting intervention may be unaffordable to deliver. However, component costs can also have implications in terms of opportunity costs (Russell, 1992): that is, when components are selected and combined, the resulting intervention may require the use of resources that could have been allocated elsewhere, such as to other useful programs. Given opportunity costs there might be good reason to select one less costly intervention over another more costly intervention, even if both of those interventions are affordable. Unlike the initial component screening approach, a posterior expected value approach can readily be used to make decisions when the optimization objective acknowledges opportunity costs.

Second, the initial component screening approach was limited to cases with a single outcome of interest. In many behavioral health areas, multiple outcome measures are necessary to capture the primary areas of importance to intervention scientists. In HIV care continuum interventions, for example, successful health promotion depends on individual behavior change in various domains (Gwadz et al., 2017). Assessing the success of an intervention, therefore, frequently involves measuring change in more than one outcome. Decision-makers may also have preferences about the outcomes of interest that place more importance on some outcomes than others. In these cases, in particular, different degrees of intervention success on different outcomes may need to be weighed carefully.

When there are multiple outcome variables of interest, determining which components have individual and/or combined effects that justify their costs becomes considerably more challenging. A particular intervention component may improve some outcome variables and, at the same time, have no effect or even undesirable effects on other outcome variables. Moreover, when combined, components may interact in ways that complicate their patterns of effects further. Components may interact synergistically, such that their combined effect on an outcome is better than the sum of their individual effects, or antagonistically, such that their combined effect on an outcome is worse than the sum of their individual effects. A particular combination of components may act synergistically on one outcome but antagonistically on another. Such complexities in optimization trial results can produce tradeoffs among outcomes, for example, such that choosing one alternative intervention over another requires trading change in one outcome for change in another outcome. A posterior expected value approach can also readily be used to make decisions based on multiple outcome variables.

The Present Study

In this article, we present decision analysis for intervention value efficiency (DAIVE), a strategy for optimization decision-making that uses a posterior expected value approach. We apply DAIVE to select optimized interventions in an empirical example from HIV care, using data from the Heart to Heart 2 study (HTH2; Gwadz et al., 2017), in which a factorial optimization trial was conducted with the goal of optimizing an intervention to move individuals along the HIV care continuum. To highlight the new possibilities for optimization that DAIVE makes available, we demonstrate DAIVE in 12 decision-making scenarios, each involving (a) one of three different optimization objectives and (b) one of four ways of defining the value of alternative interventions. The three optimization objectives incorporate either (a) no resource considerations, (b) efficiency considerations only, or (c) efficiency and affordability considerations. With the different ways of defining the value of alternative interventions, we consider decision-making based on one of the three outcome variables (described below) and based on all three outcome variables. We apply DAIVE to identify possible optimized interventions in the resulting 12 scenarios, and we show how different optimized interventions may be appropriate for different scenarios. We conclude by considering implications for intervention optimization and offering recommendations for intervention scientists using MOST who choose to apply DAIVE to select optimized interventions using their own optimization trial data.

Method

Transparency and Openness

We use data from HTH2 (Gwadz et al., 2017) to illustrate the use of DAIVE to identify optimized interventions in a variety of decision-making scenarios. Here, we describe our methods in two parts: methods of relevance to (a) the source of our empirical data, HTH2 and (b) to our applications of DAIVE to data from the HTH2 optimization trial. Data were analyzed using R Version 4.0.3 (R Core Team, 2021). The HTH2 optimization trial was preregistered on ClinicalTrials.gov (NCT02801747) and approved by the NYU IRB. Code is available in the online supplemental material A.

Inquiries about data and materials may be directed to the corresponding author.

The Empirical Illustration: HTH2

The Goal of HTH2 and the Intervention Components of Interest

The goal of the HTH2 optimization trial was to identify the combination of candidate intervention components that, while remaining affordable and efficient, best promoted important health outcomes for individuals living with HIV and experiencing barriers to engagement in HIV treatment. The optimization trial involved 512 African American, Black, and/or Latinx people living with HIV who were, at trial enrollment, neither sufficiently engaged in HIV primary care at recommended levels (assessed from medical records and quantified in terms of time without a visit or number of missed visits) nor reliably taking HIV antiretroviral therapy (ART) to the point of achieving viral suppression. For additional eligibility criteria in HTH2, we refer readers to Gwadz et al. (2017). The research team identified five experimental intervention components of interest and operationalized the components as two-level factors (Table 1). Justification for the selection of experimental components and the definition of factor levels is also provided in Gwadz et al. (2017). An additional component was included but not experimentally manipulated; instead, it was provided to all HTH2 participants. This component provided standard HIV treatment education, consistent with the recommendations of the U.S. Department of Health and Human Services (Gwadz et al., 2017), and will not be discussed further.

Experimental Design

The HTH2 trial used a 2^{5-1} fractional factorial design to estimate individual and combined effects of the factors representing the five experimental intervention components (Gwadz et al., 2017). The potential advantages of the fractional factorial design are well documented (e.g., Collins et al., 2009). HTH2's fractional factorial design yields estimates of five main effects, one for each factor, and 10 two-way interaction effects on each outcome of interest. These effects are then used to estimate expected outcomes ($\hat{Y}s$) for each of the $2^5 = 32$ combinations of factor levels.

Measurement of the Empirical Outcomes in HTH2

For the purposes of this study, we selected three outcome variables of interest from HTH2: (a) HIV viral load (*VL*), (b) a generic preference-based measure of health-related quality of life (*QOL*), and (c) engagement in HIV primary care (*Care*). Outcome 1, *VL*, a continuous, log10-transformed variable, was assessed at a commercial laboratory using a blood specimen provided by the participant (Gwadz et al., 2017) both at screening and at two follow-up assessments that took place within a 1-year period. Outcome 2, *QOL*, was measured using the six-dimensional health state classification, SF-6D (Brazier & Roberts, 2004), derived from the Short-Form 12 Health Survey (SF-12). The SF-6D, which covers a range of general health functioning and health-related *QOL* domains, strategically incorporates general population preferences for different states of health and can be interpreted in quality-adjusted life year (QALY) units (with one QALY representing one additional year of life in good health). *QOL* was measured at baseline and at three follow-ups that took place within a 1-year period. Outcome 3, *Care*, was measured using the following interview question: "In the past year, have you received care from a health care provider who specializes in treating HIV?" Participants who answered "yes" to this item in any follow-up interview were considered engaged in HIV care.

Measurement of Cost in HTH2

In the present study, we focus on the monetary costs (in U.S. dollars, 2019) required to deliver each alternative intervention, per person, from the perspective of the service provider. Each factor level in HTH2 was associated with a certain delivery cost (Table 1). Because costs were in this case additive, the per-person delivery cost for a specific alternative intervention was equal to the sum of the costs of the factor levels making up that intervention, plus the cost of the constant component ($181.51). Total delivery costs for the alternative interventions ranged from $484.24 per

Table 1
Experimental Components, Factor Levels, and Costs

Component	Brief description	Factor levels (and per-person delivery costs)
Motivational interviewing sessions	Four counseling sessions, approximately 60–90 min each, addressing health beliefs and emotions that serve as barriers to HIV care, barriers to ART, and barriers to treatment adherence	ON (*MI*; $461.98)/OFF
Focused support groups	Six group sessions over 4 months, aimed at increasing social support and reducing stigma	ON (*SG*; $502.35)/OFF
Peer mentorship	Regular interactions with a peer mentor/health coach over 4 months	ON (*PM*; $510.86)/OFF
Preadherence skill building	Individualized sessions following the HRSA guidelines aimed at promoting ART adherence and building habits	ON (*SB*; $245.02)/OFF
Navigation	Individualized menu of activities following HRSA guidelines, aimed at facilitating participants' use of health and social services by identifying and circumventing structural barriers, called navigation	Longer (*NL*; $439.52)/ Shorter (*NS*; $302.73)

Note. ART = antiretroviral therapy; HRSA = Health Resources and Services Administration.

person (the "minimal intervention," consisting of the shorter duration of navigation) to $2,341.24 per person (the "complete intervention," consisting of motivational interviewing, skill-building, peer mentoring, focused support groups, and the longer duration of navigation).

Applying DAIVE to Data From HTH2

DAIVE uses a posterior expected value approach (Strayhorn et al., 2023), which consists of the following steps. The starting point is the data obtained in the factorial optimization trial on each outcome variable to be used in decision-making. Data on each empirical outcome are analyzed using Bayesian factorial analysis of variance. This approach produces a posterior distribution corresponding to each main effect and interaction effect to be estimated. These are then used to obtain posterior distributions for the expected outcomes, or $\hat{Y}s$, on each outcome variable for each alternative intervention under consideration.

When there are multiple empirical outcomes that decision-makers care about, a value function is used to combine the outcomes, yielding a posterior distribution for the expected value of each alternative intervention. The value function reflects decision-maker preferences about the variables of interest (i.e., which outcomes are important—and how important, relative to one another). As will be illustrated below, different value functions offer different ways of defining the value of the alternative interventions under consideration (i.e., what is the most-preferred outcome or combination of outcomes for the interventions?).

Finally, selection of optimized interventions is based on comparisons among (a) the expected values associated with each alternative intervention and, when called for by the optimization objective, (b) the costs associated with each alternative intervention. This selection step relies on point estimates for expected values, as consistent with precedents in the decision science literature, in which there are, in the words of Claxton (1999), "conceptually separate steps": first, selecting an alternative to proceed with, given available evidence and second, determining whether more evidence is needed about the performance of that alternative. The first step "should be based only on the mean net benefits irrespective of whether differences are statistically significant" (Claxton, 1999, p. 341); the second, based on the degree of uncertainty around that alternative (and possibly others). The challenges we focus on in this article—that is, applying DAIVE to select an optimized intervention—fall within the first of these conceptually separate steps. In MOST, selection of an optimized intervention is followed by deliberation about whether the optimized intervention is promising enough to justify further evaluation (Collins, 2018), as consistent with the second step; we return to this in the "Discussion" section.

We estimated expected outcomes in HTH2 using the brms package (Bürkner, 2021). As detailed further in the online supplemental material A, we estimated main and interaction effects on *VL* at follow-up using Bayesian regression, equipped with the brms default priors, controlling for (a) *VL* at screening and (b) the number of days that elapsed between the baseline and follow-up assessments. We estimated main and interaction effects on *QOL* using Bayesian mixed effects regression, also equipped with brms default priors, that incorporated repeated measures of *QOL*. As a result, the main and interaction effects estimated can be interpreted as effects on average *QOL* over 1 year of follow-up. We estimated main and

Figure 1
Optimization Objectives and Scenarios of Interest

Optimization Objective 1 ☒ no restrictive limit on affordability ☒ no consideration of opportunity costs	**Optimization Objective 2** ☒ no restrictive limit on affordability ☑ consideration of opportunity costs	**Optimization Objective 3** ☑ restrictive limit on affordability ☑ consideration of opportunity costs
Scenario 1a Value defined in terms of *VL* only.	**Scenario 2a** Value defined in terms of *VL* only.	**Scenario 3a** Value defined in terms of *VL* only.
Scenario 1b Value defined in terms of *QOL* only.	**Scenario 2b** Value defined in terms of *QOL* only.	**Scenario 3b** Value defined in terms of *QOL* only.
Scenario 1c Value defined in terms of *Care* only.	**Scenario 2c** Value defined in terms of *Care* only.	**Scenario 3c** Value defined in terms of *Care* only.
Scenario 1d Value defined in terms of all three outcomes.	**Scenario 2d** Value defined in terms of all three outcomes.	**Scenario 3d** Value defined in terms of all three outcomes.

Note. VL = HIV viral load outcome; QOL = generic preference-based measure of health-related quality of life; Care = engagement in HIV primary care outcome.

interaction effects on *Care* using Bayesian logistic regression (again equipped with brms default priors), controlling for *VL* at screening. (See online supplemental material A for more information about these analyses, including code.) We defined three optimization objectives (Figure 1) that required different approaches to handling cost and four value functions (described later in this section) that reflected different ways decision-makers may define value in terms of these outcome variables of interest.

Three Optimization Objectives

Optimization objective 1 is met by identifying the intervention that maximizes the value function, with no consideration of costs (i.e., with no restrictive limit on affordability and no acknowledgment of opportunity costs). Optimization objective 2 is met by identifying and then selecting from the set of "value-efficient" interventions. To define value efficiency, it is first necessary to define dominance. One intervention dominates a second intervention if the first has higher expected value and lower costs than the second (Drummond et al., 2015). The set of nondominated interventions is value-efficient in the economic sense that it is not possible to achieve a more highly valued outcome without expending additional resources (see, e.g., Varian, 2010). Once a set of value-efficient interventions is identified under Optimization objective 2, the next step involves selecting the most-preferred intervention from among the set. Selection of the most preferred intervention from among the set of value-efficient interventions involves systematic consideration of each value-efficient intervention, from least costly to most costly, with consideration of opportunity costs. Finally, Optimization objective 3 is met by identifying and then selecting from the set of value-efficient interventions that are also affordable in the sense that they cost less than a hypothetical $1,500 program-specific budget. Again, the next step involves selecting the most-preferred intervention from among the set, with consideration of opportunity costs.

Four Ways of Defining the Value of the Alternative Interventions

For the purposes of this study, we defined four multiattribute value functions based on simple weighted sums that used different sets of weights: three that assigned positive weight to only one outcome and zero to the others (value functions a through c) and one that assigned positive weight to all three outcomes of interest (value function d). Each of these multiattribute value functions shows how much performance on one outcome a decision-maker is willing to trade for reduced performance on another outcome. The simple weighted sum is just one of many possible value functions that can be used in DAIVE. We selected the weighted sum for its (a) widespread use in MCDA (Thokala et al., 2016); (b) ease of use and straightforward interpretation, relative to alternatives; and (c) potential generalizability to various contexts.

With value functions a through c, we imagined that the decision-makers were interested in basing their selection of an optimized intervention on a single primary outcome from among the three outcome variables. As described further below, we rescaled the outcomes such that they were all on similar 0-to-1 scales where a higher score was better. With value function a, the primary outcome was *VL*, so all weight was given to outcome *VL*: $\mathrm{V} = \mathrm{Y}_{\mathrm{VL}}$. With value function b, all weight was given to *QOL*: $\mathrm{V} = \mathrm{Y}_{\mathrm{QOL}}$. With value function c, all weight was given to *Care*: $\mathrm{V} = \mathrm{Y}_{\mathrm{Care}}$. These value functions reflect the decision-maker preference that a higher value intervention is one that is associated with a better expected mean outcome (better *VL*, better *QOL*, or better *Care*, respectively)—and with no willingness to trade performance on that outcome for performance on another outcome.

With value function d, we imagined that decision-makers wanted to base decision-making on all three outcome variables—and that, of the three outcome variables, *VL* was deemed most important, followed by *QOL*, followed by *Care*. There are many alternative strategies for picking outcome weights; for this study, we chose a swing weighting exercise (described in the online supplemental material B), which gave us value function d: V = 0.6(VL)+ 0.3(SF6D) + 0.1(Care). Value function d represents the decision-maker preference that a higher value intervention is one with a better linear combination of expected mean outcomes.

Estimating Expected Value With the Four Value Functions

True mean outcomes for the 32 alternative interventions under consideration are, of course, unknown. However, collecting data D (as collected in a factorial optimization trial) and applying a statistical model with effect parameters θ (such as a set of generalized linear models for the outcomes incorporating identifiable main and interaction effects θ_j) yields estimates for these mean outcomes. We used Markov chain Monte Carlo (MCMC) to obtain samples $m = 1 \ldots M$ from the parameter posterior $\theta_{j[m]} \sim P(\theta_j|D)$ for each outcome *j*. Then for each parameter posterior sample draw for each outcome, we calculated the conditional mean outcome $\hat{Y}_{ij}(\theta_{j[m]})$; rescaled the conditional mean outcomes via the swing weighting exercise; applied the given scenario's value function to the vector of conditional mean outcomes; and took the average to obtain the expected value of alternative intervention *i*:

$$E[V(\hat{Y}_i, \omega)] = \frac{1}{M}\sum_{m=1}^{M} V(\hat{Y}_{i1}(\theta_{1[m]}), \ldots \hat{Y}_{iJ}(\theta_{J[m]})).$$

Results

Table 2 provides costs and expected values for the 32 alternative interventions with value functions a through d. Decision-making under the different optimization objectives, then, is based on results in Table 2, as follows.

Optimization Objective 1: Identify the Intervention That Maximizes the Value Function

With Optimization objective 1, selection of an optimized intervention is based on a comparison of expected values for the 32 alternative interventions. With value functions b and d, the intervention that maximizes the value function is the one that contains all components at the higher levels (*MI, SB, PM, SG, NL*, i.e., the "complete intervention"), whereas a suggests including only motivational interviewing, skill-building, peer mentoring, and the longer duration of navigation (*MI, SB, PM, NL*), and c suggests an intervention that contains only peer mentoring and the shorter duration of navigation (*PM, NS*). Thus, the four different value functions yield three different optimized interventions under Optimization objective 1.

Optimization Objective 2: Identify and Select From the Set of Value-Efficient Interventions

With Optimization objective 2, selection of an optimized intervention is based on a comparison of the expected values and costs associated with the subset of alternative interventions that are value efficient, relative to the full set of alternatives, with all alternative interventions assumed to be affordable. Consider Scenario 2a, in which the decision-maker has selected *VL* as the primary outcome and used value function a to estimate expected values. Figure 2 shows a plot of costs versus expected values for this scenario. As can be seen in the zoomed-in region of the plot, each point represents an alternative intervention containing some combination of factor levels. The intervention including motivational interviewing, skill-building, peer mentoring, and the longer navigation (*MI, SB, PM, NL*), which maximizes the value function in this scenario (as in Scenario 1a), is highlighted.

Figure 3 plots cost versus expected value for Scenarios 2a through 2d; the value-efficient interventions in each scenario are identified and connected with a solid line. Together, the identified interventions in each plot make up the plot's "value efficiency frontier," which can be observed as a sort of "boundary" in the plotted points. By definition, the value efficiency frontier begins with the least expensive alternative—in this case, the intervention that includes only the shorter duration of navigation (*NS*)—and ends with the intervention that maximizes the value function. Any additional alternatives on the frontier are those that are not dominated by any other intervention. Figure 3 illustrates how the frontier of efficiency can be very different in both shape and composition when different definitions of value are used.

To see how the frontier of efficiency can be helpful in decision-making, consider Scenario 2a again, starting with that least-expensive alternative, which includes the shorter duration of navigation (*NS*). Next, move up the solid line to the next intervention, which includes the longer duration of navigation (*NL*). This intervention produces an improvement in value, relative to the least-expensive alternative, and the incremental cost of the improvement is reflected in the slope of the line segment connecting the two

Table 2
Costs and Expected Values (With 95% Credible Intervals) for the 32 Alternative Interventions With Value Functions a Through d

		a V = *VL*		b V = *QOL*		c V = *Care*		d V = 0.6**VL* + 0.3**QOL* + 0.1**Care*	
Intervention	Cost ($)	EV	Lower, upper	EV	Lower, upper	EV	Lower, upper	EV	Lower, upper
NS	484	0.438	[0.214, 0.660]	0.417	[0.221, 0.609]	0.809	[0.516, 0.963]	0.476	[0.329, 0.621]
MI, NS	946	0.391	[0.179, 0.606]	0.498	[0.306, 0.686]	0.739	[0.484, 0.910]	0.464	[0.324, 0.603]
SG, NS	987	0.606	[0.381, 0.829]	0.269	[0.075, 0.461]	0.808	[0.558, 0.956]	0.531	[0.385, 0.676]
MI, SG, NS	1,449	0.530	[0.307, 0.749]	0.450	[0.256, 0.649]	0.828	[0.567, 0.961]	0.542	[0.397, 0.685]
PM, NS	995	0.283	[0.079, 0.490]	0.403	[0.212, 0.587]	0.941	[0.798, 0.999]	0.396	[0.263, 0.529]
MI, PM, NS	1,457	0.368	[0.160, 0.578]	0.600	[0.411, 0.788]	0.929	[0.794, 0.989]	0.502	[0.367, 0.639]
SG, PM, NS	1,497	0.407	[0.190, 0.619]	0.351	[0.163, 0.531]	0.791	[0.480, 0.959]	0.436	[0.294, 0.575]
MI, SG, PM, NS	1,959	0.462	[0.256, 0.666]	0.647	[0.470, 0.827]	0.819	[0.583, 0.958]	0.559	[0.425, 0.691]
SB, NS	729	0.374	[0.164, 0.579]	0.553	[0.389, 0.715]	0.796	[0.600, 0.933]	0.476	[0.342, 0.608]
MI, SB, NS	1,191	0.257	[0.039, 0.475]	0.479	[0.298, 0.670]	0.478	[0.033, 0.809]	0.348	[0.203, 0.496]
SB, SG, NS	1,231	0.628	[0.403, 0.851]	0.507	[0.309, 0.700]	0.825	[0.546, 0.961]	0.616	[0.469, 0.761]
MI, SB, SG, NS	1,694	0.481	[0.233, 0.731]	0.533	[0.327, 0.742]	0.727	[0.452, 0.916]	0.525	[0.364, 0.687]
SB, PM, NS	1,240	0.404	[0.188, 0.621]	0.507	[0.328, 0.694]	0.906	[0.727, 0.986]	0.493	[0.354, 0.633]
MI, SB, PM, NS	1,702	0.417	[0.203, 0.632]	0.549	[0.361, 0.742]	0.755	[0.494, 0.932]	0.496	[0.355, 0.637]
SB, PM, SG, NS	1,742	0.613	[0.383, 0.842]	0.558	[0.366, 0.763]	0.712	[0.437, 0.899]	0.608	[0.459, 0.757]
MI, SB, PM, SG, NS	2,204	0.597	[0.364, 0.833]	0.700	[0.507, 0.897]	0.542	[0.106, 0.848]	0.621	[0.414, 0.643]
NL	621	0.551	[0.378, 0.726]	0.399	[0.240, 0.560]	0.740	[0.531, 0.896]	0.529	[0.414, 0.643]
MI, NL	1,083	0.628	[0.411, 0.849]	0.505	[0.318, 0.689]	0.705	[0.344, 0.918]	0.601	[0.457, 0.745]
SG, NL	1,123	0.530	[0.325, 0.735]	0.218	[0.041, 0.396]	0.842	[0.602, 0.963]	0.475	[0.341, 0.608]
MI, SG, NL	1,585	0.578	[0.377, 0.778]	0.424	[0.249, 0.599]	0.895	[0.725, 0.984]	0.570	[0.440, 0.700]
PM, NL	1,132	0.452	[0.232, 0.671]	0.410	[0.224, 0.599]	0.893	[0.701, 0.983]	0.491	[0.350, 0.632]
MI, PM, NL	1,594	0.660	[0.434, 0.885]	0.631	[0.435, 0.822]	0.880	[0.672, 0.984]	0.677	[0.531, 0.823]
SG, PM, NL	1,634	0.386	[0.184, 0.588]	0.325	[0.144, 0.511]	0.766	[0.54, 0.919]	0.413	[0.280, 0.545]
MI, SG, PM, NL	2,096	0.565	[0.344, 0.787]	0.647	[0.463, 0.829]	0.839	[0.591, 0.963]	0.621	[0.478, 0.764]
SB, NL	866	0.441	[0.234, 0.647]	0.590	[0.409, 0.775]	0.784	[0.475, 0.945]	0.525	[0.389, 0.660]
MI, SB, NL	1,328	0.447	[0.243, 0.650]	0.541	[0.361, 0.720]	0.607	[0.335, 0.824]	0.493	[0.359, 0.627]
SB, SG, NL	1,368	0.505	[0.304, 0.703]	0.513	[0.336, 0.681]	0.901	[0.732, 0.988]	0.554	[0.424, 0.618]
MI, SB, SG, NL	1,830	0.481	[0.258, 0.706]	0.563	[0.379, 0.763]	0.883	[0.677, 0.981]	0.553	[0.409, 0.697]
SB, PM, NL	1,376	0.526	[0.283, 0.768]	0.570	[0.372, 0.780]	0.857	[0.618, 0.983]	0.578	[0.421, 0.734]
MI, SB, PM, NL	1,838	0.662	[0.426, 0.897]	0.637	[0.436, 0.837]	0.727	[0.36, 0.931]	0.663	[0.508, 0.816]
SB, PM, SG, NL	1,879	0.545	[0.323, 0.768]	0.589	[0.392, 0.781]	0.754	[0.414, 0.941]	0.582	[0.436, 0.729]
MI, SB, PM, SG, NL	2,341	0.652	[0.361, 0.948]	0.754	[0.522, 0.989]	0.706	[0.35, 0.936]	0.689	[0.500, 0.875]

Note. Costs (in US dollars, 2019) are rounded to the nearest dollar. "EV" = expected value as estimated using a given value function ("V"); "Lower" = lower bound of a given 95% credible interval; "Upper" = upper bound of a given 95% credible interval; VL = HIV viral load outcome; QOL = generic preference-based measure of health-related quality of life; Care = engagement in HIV primary care outcome; MI = motivational interviewing is set to "On"; SB = skill-building is set to "On"; PM = peer mentoring is set to "On"; SG = support groups is set to "On"; NL = navigation is set to its longer duration; NS = navigation is set to its shorter duration.

dots (the dot for *NS* and the dot for *NL*). In this case, the shallow slope of this line reflects that the increase in cost is modest. Now compare this slope to that of the next segment, the one representing the improvement in value and increase in cost associated with moving to the intervention consisting of motivational interviewing and the longer duration of navigation (*MI, NL*). This slope is steeper, reflecting that the increase in value is relatively costlier (similar to the colloquial expression referring to the price of a consumer item under consideration as "steep"). The online supplemental material B contains several worked examples that illustrate the computations in more detail.

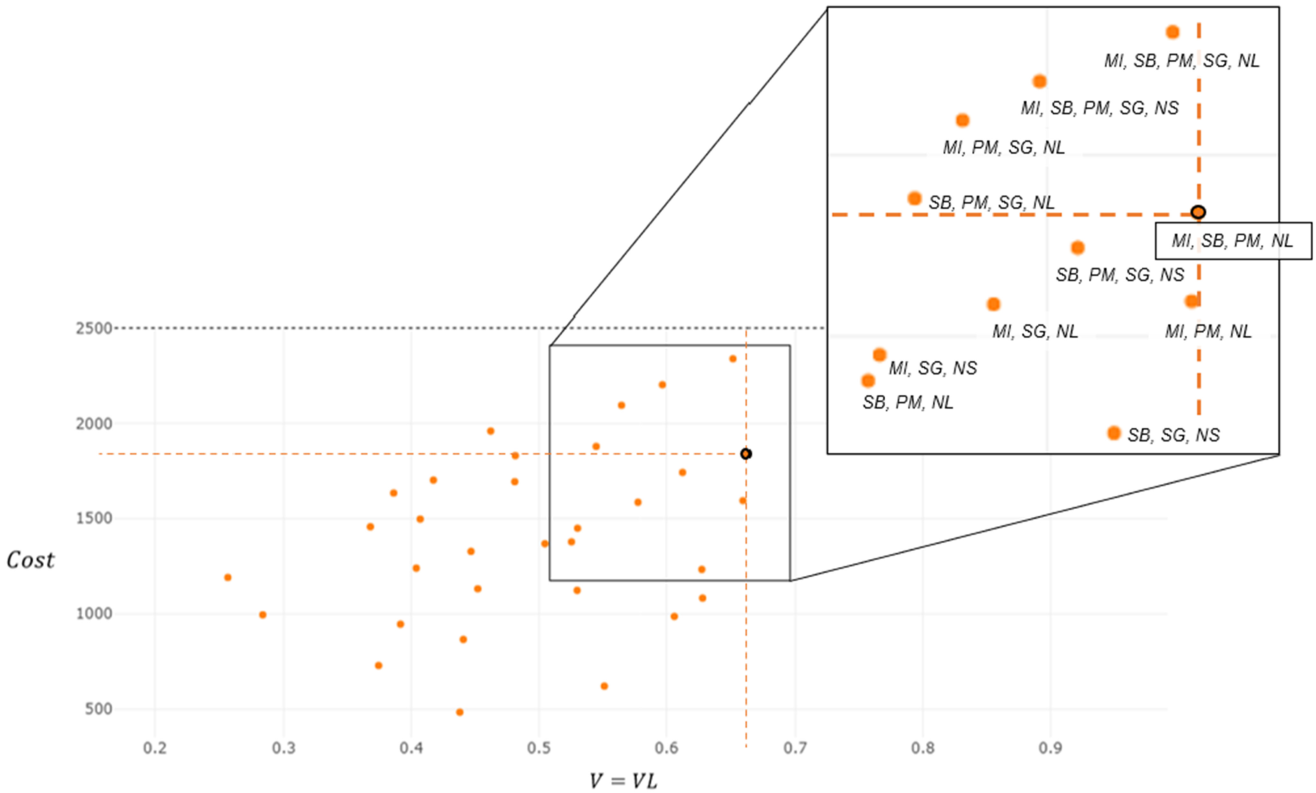
The decision-maker can work up or down the value efficiency frontier to decide which intervention offers the best balance of expected value and cost, with consideration of opportunity costs. If a line segment on the frontier is sufficiently steep, that suggests that the small increase in expected value for one alternative versus another comes at a large increase in cost—and perhaps, that those additional resources would be better devoted elsewhere. In Scenario 2a, for example, there may be a reason to choose an alternative other than the one that maximizes the value function, given opportunity costs.

Optimization Objective 3: Identify and Select From the Set of Value-Efficient Interventions That Can Be Delivered for Less Than $1,500 Per Person

With Optimization objective 3, decision-making involves a comparison of costs and expected values for alternative interventions that are value-efficient relative only to the other *affordable* alternatives, with affordability this time defined as costing less than $1,500 per person in delivery costs. Figure 4 shows plotted costs versus expected values for four more scenarios (3a through 3d, with Objective 3 and value functions a through d, respectively). In these plots, interventions that fall within the shaded region are unaffordable and therefore eliminated from consideration. As before, the value efficiency frontier is indicated by connecting the value-efficient alternatives with a solid line. Comparison of Figures 2 and 3 shows that eliminating unaffordable alternatives from consideration can change the shape and composition of the frontier of efficiency. The differences are particularly striking when the b and d value functions are used. Now that the "complete" intervention is unaffordable, the frontier in Scenario 3b adds a new intervention

Figure 2

Per Person Delivery Costs Versus Expected Values for the 32 Alternative Interventions in One Scenario



Note. Each dot represents an alternative intervention. *MI* indicates that motivational interviewing is set to "On"; *SB*, that skill-building is set to "On"; *PM*, that peer mentoring is set to "On"; and *SG*, that support groups is set to "On." *NL* indicates that navigation is set to its longer duration; *NS*, that navigation is set to its shorter duration. The intervention that maximizes this value function (*MI, SB, PM, NL*) is highlighted with a box. See the online article for the color version of this figure.

consisting of motivational interviewing, peer mentoring, and the shorter duration of navigation (*MI, PM, NS*) into consideration. The frontier in Scenario 3d, similarly, adds a new alternative consisting of skill-building, support groups, and the shorter duration of navigation (*SB, SG, NS*). In each of these scenarios, the intervention added moved onto the frontier of efficiency, and therefore into consideration, only after the interventions deemed unaffordable were removed as alternatives.

Discussion

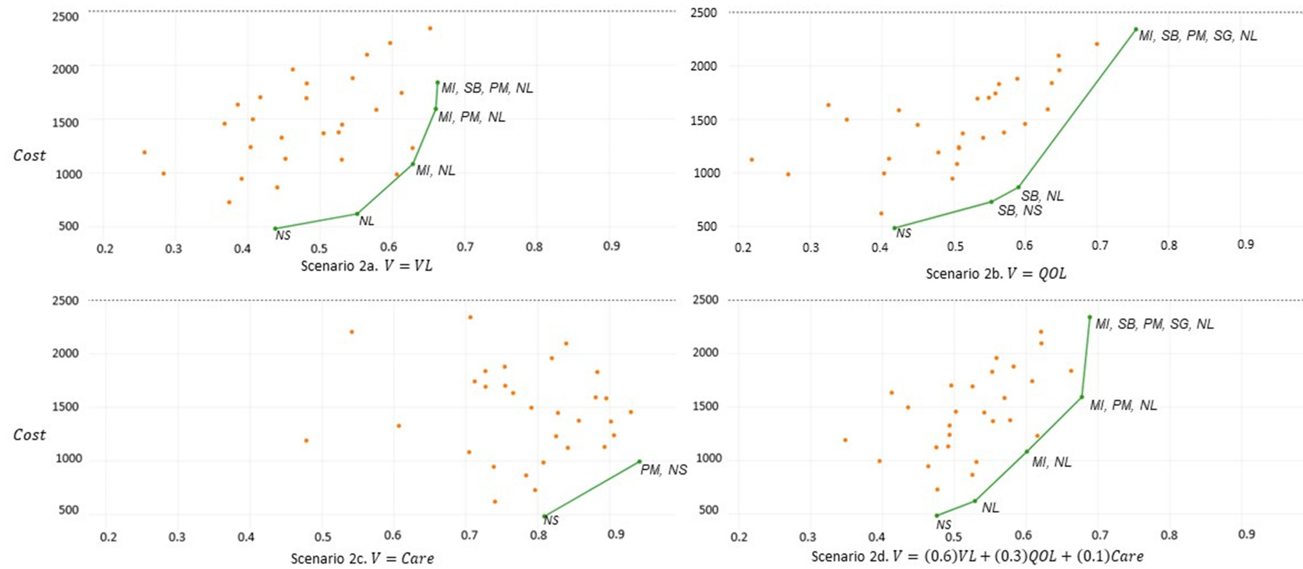
In MOST, the optimized intervention is one that, relative to the alternatives under consideration, is expected to best accomplish intervention *EASE*, balancing effectiveness with affordability, scalability, and/or efficiency criteria. The meaning assigned to the *EASE* criteria will vary according to decision-makers' objectives and preferences—and, accordingly, so too may the choice of optimized intervention. One advantage of a posterior expected value approach to selecting an optimized intervention is the ability to flexibly accommodate a variety of optimization objectives and decision-maker preferences, including preferences about more than one outcome variable. In this article, we illustrate the use of DAIVE to select optimized interventions based on empirical data from an optimization trial (Gwadz et al., 2017), and we show how the choice of optimized intervention can vary with different optimization objectives and different value functions reflecting decision-maker preferences about outcome variables.

With Optimization objective 1, the goal was to identify the intervention that maximized the value function. Notably, in this empirical illustration, optimization based on different selected primary outcome variables resulted in different optimized interventions. Why were there such differences in the selection of an optimized intervention with different single outcome value functions? In HTH2, the experimental factors had different patterns of effects, including main effects and interaction effects, on different outcome variables. In optimization trials in which the experimental factors have more similar effects on different outcome variables, more consistency in decision-making across analogous scenarios would be expected. Still, this empirical example demonstrates that tradeoffs in performance on different outcomes are possible and perhaps the norm in actual applications of intervention optimization. DAIVE offers a framework for making decisions consistent with decision-maker preferences when such tradeoffs occur.

Optimization objectives 2 and 3 incorporated the concept of intervention value efficiency—and the idea that any intervention that falls on the value efficiency frontier could be a contender for the optimized intervention, depending on opportunity costs. With these

Figure 3

Per Person Delivery Costs Versus Expected Values for the 32 Alternative Interventions in Four Scenarios



Note. Each scenario uses a different definition of value. Each dot represents an alternative intervention. *MI* indicates that motivational interviewing is set to "On"; *SB*, that skill-building is set to "On"; *PM*, that peer mentoring is set to "On"; and *SG*, that support groups is set to "On." *NL* indicates that navigation is set to its longer duration; *NS*, that navigation is set to its shorter duration. *MI, SB, PM, SG*, and *NL* are the "complete intervention." *NS* is the "minimal intervention." In a given scenario, the value efficiency frontier is highlighted with a solid line; each intervention on this line is value efficient.

optimization objectives, the goal was to identify and select from the set of value-efficient interventions, without or with a restrictive budget limit defining affordability, respectively. In some cases (3b and 3d), redefining affordability meant that a previously dominated intervention became value-efficient when the intervention that dominated was deemed unaffordable.

Consider again the results in Scenario 3d, with the multiple outcomes value function. Scenario 3d illustrates one reason why, when it is necessary to make changes in response to reductions in implementation resources, it is often a good idea to base the changes on intervention optimization. Suppose a decision-maker had used the results shown in Figure 2 to select an intervention based on Scenario 2d, selecting the alternative consisting of motivational interviewing, peer mentoring, and the longer duration of navigation (*MI, PM, NL*). Now suppose the decision-maker learns that the relevant budget for eventual implementation of the intervention has been cut; as a result, this alternative, along with all others costing more than $1,500, is off the table. It might be tempting for the decision-maker to simply select a reduced intervention consisting of a subset of the originally selected alternative. In fact, this would not necessarily be a bad strategy in this case; Figure 4 shows that removing peer mentoring would produce an intervention (*MI, NL*) that is value-efficient. However, Figure 4 also shows that, although it is a bit counterintuitive, a better alternative might be an entirely different intervention, made up of skill-building, support groups, and the shorter duration of navigation (*SB, SG, NS*). This alternative costs more but is within the budget limit, and it is expected to deliver more in terms of expected value. Moreover, without the information from the optimization trial, the ad hoc modification of the intervention that was initially chosen in an effort to achieve affordability could easily have been counterproductive. For example, the ad hoc elimination of motivational interviewing, instead of peer mentoring, would result in an intervention that is not value-efficient—and probably no type of ad hoc modification would suggest the intervention made up of skill-building, support groups, and the shorter duration of navigation (*SB, SG, NS*).

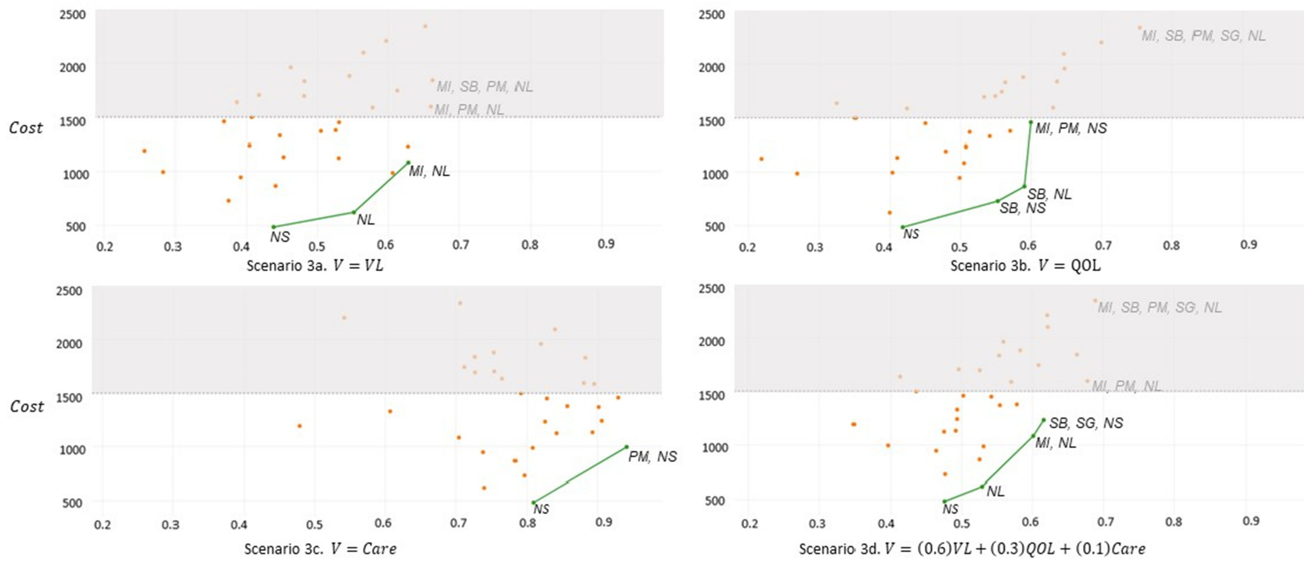
Still, though we argue that this new alternative (*SB, SG, NS*) should be considered value-efficient under this sort of affordability limit, and with value efficiency defined strictly in terms of the available resources, the finding also remains that there would at least theoretically be less steepness in other choices (e.g., that alternative consisting of motivational interviewing, peer mentoring, and the longer duration of navigation) if they were affordable. This may suggest that the strict budget of $1,500 per person should be renegotiated. In the present empirical illustration, the case for budget renegotiation is particularly strong, given that the cutoff was selected arbitrarily, for illustration purposes. Of course, we recognize that in practice, intervention scientists may not have any direct involvement in the negotiation of budget allocations. In cases like Scenario 3d, best practice may involve reporting not only the selection of an optimized intervention, given the strict upper limit on affordability, but also a full set of alternatives so they will be available should consideration be given to increasing the budget.

Choosing Outcome Weights for Use in the Selection of an Optimized Intervention

In the present study, we used a simple weighted sum value function that incorporated hypothetical preferences about three outcome variables of interest. If we had used different weights, reflecting different degrees of relative importance in outcome variables, we would have likely obtained different results. This is appropriate; in different scenarios, different interventions may be better contenders for the

Figure 4

Per Person Delivery Costs Versus Expected Values for the 32 Alternative Interventions in Four Scenarios, With an Upper Limit on Affordability ($1,500)



Note. Each scenario uses a different definition of value. Each dot represents an alternative intervention. *MI* indicates that motivational interviewing is set to "On"; *SB*, that skill-building is set to "On"; *PM*, that peer mentoring is set to "On"; and *SG*, that support groups is set to "On." *NL* indicates that navigation is set to its longer duration; *NS*, that navigation is set to its shorter duration. *MI, SB, PM, SG*, and *NL* are the "complete intervention." *NS* is the "minimal intervention." With a restrictive affordability limit of $1,500 per person, interventions that fall within the gray shading are unaffordable and removed from consideration. In a given scenario, the value efficiency frontier is highlighted with a solid line; each intervention on this line is value efficient.

optimized intervention. In practice, we recommend that outcome variable weights be chosen a priori, for example, via a preliminary swing weighting exercise. However, the systematic variation of weights can also be a useful exercise. For example, even when decision-makers have decided upon a set of outcome weights, it can be beneficial for decision-makers to also (a) observe the results in the single primary outcomes cases, (b) check whether decisions are robust to small changes in weights, and/or (c) consider alternative plausible sets of weights, such as the equal-weight case in which each outcome is given the same weight. Such exercises may be particularly useful in helping to establish consensus about how the outcome variables are to be weighted when more than one decision-maker must work together to arrive at a single optimized intervention.

Choosing Costs for Use in the Selection of an Optimized Intervention

In this illustration of DAIVE, we incorporated information about the per-person delivery costs associated with each alternative intervention (from the perspective of the service provider), and we used this information to make efficiency and affordability determinations. Other costs or resource considerations could also be used for these purposes, as applicable, depending on decision-makers' priorities. For example, in some cases, time may be a more relevant constraint than monetary cost, whether in terms of opportunity costs, such that the interventions that are value efficient in their use of the available time are compared; or a strict upper limit; or both. Choosing costs for optimization purposes is a matter of defining the metric(s) of most relevance to determining which intervention components are worth advancing further.

Additional cost-related analyses can also be conducted with the results of a factorial optimization trial, including more formal cost-effectiveness analysis. The opportunity costs we consider in the present illustration do form the basis of traditional benefit-cost and cost-effectiveness analysis (Danzon et al., 2018), and optimization objectives including opportunity costs can be considered a form of provider-perspective cost-effectiveness analysis. This is different from societal or healthcare sector benefit–cost or cost-effectiveness analysis, which includes the resource consequences of downstream effects associated with changed behavior, modified course of disease, etc. (Neumann et al., 2016). The cost-related determinations we make in the present illustration are not intended to replace other forms of economic analysis that take other perspectives; rather, they can be considered complementary.

Progressing to Next Steps in MOST

As noted previously, the optimization phase in MOST is followed by an evaluation phase in which the selected optimized intervention is evaluated further. Of course, it makes sense to proceed with evaluation only if there is sufficient evidence that the selected optimized will be worth additional experimentation. Once an optimized intervention is selected, intervention scientists may want to consider not only the magnitude of the expected outcome(s) associated with the optimized intervention but also the uncertainty around those outcomes (e.g., in the form of a credible interval). If the selection of an optimized intervention was based on expected value estimates, then those estimates can also be converted back to individual outcomes—that is, on the original outcome metrics—for ease of interpretation. One of the advantages of DAIVE's Bayesian paradigm is the opportunity to make probabilistic statements about point estimates that communicate uncertainty in a way that may be readily interpretable by, and helpful for, decision-makers; investigating how decision-makers should approach the consideration of uncertainty in progressing from the optimization phase to the evaluation phase is an important future direction. One possibility involves using value of information analysis (e.g., Wilson, 2015) to investigate whether narrowing the uncertainty around one or more point estimates—that is, for one optimized intervention or maybe for multiple interventions on a value efficiency frontier—is worth the additional research resources.

Limitations and Additional Future Directions

We consider decision-making based on the results of the HTH2 optimization trial in a variety of realistic scenarios, but we do not select a single, definitive optimized intervention in any of these scenarios. In practice, selecting a single optimized intervention would require more careful elicitation of the preferences of all involved decision-makers. There are many well-established methods for preference elicitation (e.g., de Bekker-Grob et al., 2012; Louviere, 2008; Salloum et al., 2017). As noted above, in optimization phase decision-making there may be good reason to both establish preferences a priori and carefully vary outcome variables and outcome weights, for example, to explore the robustness of the decisions that result. Future work could inform best practices in this area. Moreover, in practice decisions may have to be made by multiple decision-makers, some (or all) of whom may have different preferences about the outcome variables of interest. In such cases, there may be a need not only to elicit preferences but also to come to a consensus, such that a single value function can be agreed upon.

For this study, we assumed decision-makers were members of the research team who conducted the optimization trial and were responsible for selecting an optimized intervention to advance further. We also assumed that it was the decision-maker's preferences in a given scenario that informed the optimization objective and value function. In some cases, it may also be worth systematically eliciting and incorporating preferences from additional interested parties, including payors, policymakers, intervention implementers and participants, and so on. It may sometimes be worth more directly including some additional interested parties in the selection of an optimized intervention; incorporating methods from the stakeholder engagement literature (e.g., Byrne, 2019; Salloum et al., 2017) is an intriguing area for future research.

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