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Applying the Multiphase Optimization Strategy for the Development of Optimized Interventions in Palliative Care

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Abstract

Recent systematic reviews and meta-analyses have reported positive benefit of multicomponent "bundled" palliative care interventions for patients and family caregivers while highlighting limitations in determining key elements and mechanisms of improvement. Traditional research approaches, such as the randomized controlled trial (RCT), typically treat interventions as "bundled" treatment packages, making it difficult to assess definitively which aspects of an intervention can be reduced or replaced or whether there are synergistic or antagonistic interactions between intervention components. Progressing toward palliative care interventions that are effective, efficient, and scalable will require new strategies and novel approaches. One such approach is the Multiphase Optimization Strategy (MOST), a framework informed by engineering principles, that uses a systematic process to empirically identify an intervention comprised of components that positively contribute to desired outcomes under real-life constraints. This article provides a brief overview and application of MOST and factorial trial design in palliative care research, including our insights from conducting a pilot factorial trial of an early palliative care intervention to enhance the decision support skills of advanced cancer family caregivers (Project CASCADE).

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Keywords

Multiphase Optimization Strategy; factorial experiment; intervention development; clinical trials

Introduction

Among the biggest obstacles to advancing the palliative care scientific evidence base is determining active intervention components of "bundled" multicomponent interventions.[1–3] Despite positive benefits to patient and family caregivers, a major limitation highlighted in palliative care trial reviews and meta-analyses has been the lack of clarity about which intervention components and in what combination make the intervention effective.[4–7] Additionally, multicomponent interventions can be resource-intensive and costly, which limits their efficiency, economy, and scalability. Secondary analyses of palliative care trial data have yielded insights into intervention components and mechanisms of action; however, such analyses rely on observational data that generate only tentative conclusions. This predicament is significant because much time, resources, and money is spent trying to develop and improve palliative care interventions.

Hence, the purpose of this study was to provide a potential solution to this issue in the palliative care field and provide an overview of the Multiphase Optimization Strategy (MOST), an engineering-inspired, systematic approach to developing and testing multicomponent interventions.[8–11] In MOST, optimization trials, using designs such as the factorial trial, are used to provide information about what intervention components produce the best outcomes. Optimization trial designs complement the traditional randomized controlled trial (RCT) as they address different research questions.[10] While MOST has increasingly been employed in diverse research spaces such as HIV,[12] mental health promotion,[13] alcohol and drug prevention programs,[14] cardiovascular rehabilitation,[15] and physical activity and weight loss,[16,17] their use in palliative care has been limited.[18] This paper aims to explain how MOST may be applied in palliative care research to spur a new intervention development and testing pipeline, producing interventions that are not only effective but also efficient, economical, and scalable.

In this paper, we first describe the MOST framework and the primary principles underlying its approach. We then describe and outline the activities in the three phases of MOST (preparation, optimization, and evaluation), the role of the conceptual model, and factorial trial design description. We then specify the general approach to data analysis, power, sample size considerations, and interpretation. The discussion concludes by providing several insights based on our team's experiences conducting a pilot factorial trial of an early palliative care intervention to enhance the decision support skills of advanced cancer family caregivers (Project CASCADE), including methodological and logistical considerations within MOST. While this paper does not describe a wholly new methodological approach, it demonstrates the application of the MOST framework in palliative care and provides considerations for palliative care researchers wanting to pursue new directions in intervention development and testing.

The Multiphase Optimization Strategy (MOST)

Many interventions in palliative care (and in general) may be conceptualized as an assemblage or "'bundle" of components, where a component is a distinct part of an intervention that can be separated out for evaluation.[19] Components might include the program content of an intervention (e.g., educational topics on symptoms, medications, advance care planning) and the level of that content (e.g., single versus multiple sessions). Other intervention components might include delivery mode (e.g., in-person, telehealth, text messaging), interventionist types (e.g., physician, nurse, social worker, lay person), aspects of dissemination and implementation (e.g., virtual learning collaborative, technical assistance), behavior change techniques (e.g., motivational interviewing, talk therapy), timing (e.g., early vs. later), and features that promote adherence or fidelity (e.g., text messages, incentives).

In traditional approaches to multicomponent intervention development, components are "bundled" together and evaluated in an RCT. Typically there are two or more arms with one arm receiving a "bundled" intervention and another arm receiving a comparator intervention or usual care. The research question becomes: "Is the 'bundled' intervention more effective compared to the comparator intervention or usual care?" If the differences in outcomes among groups are found to be statistically significant and in favor of the intervention, the intervention is deemed effective. While the RCT remains important for determining effectiveness, the intervention is evaluated as a package during the RCT, and the results cannot discriminate which components were responsible for the beneficial effects. Of note, while components of an intervention could be tested individually in an RCT by comparing different versions of a "bundled" intervention that vary in terms of content, level, or delivery, this approach would be highly inefficient. Additionally, traditional approaches can determine neither individual component performance on the outcome of interest nor how components worked together (i.e., synergistic or antagonistic interactions). Relatedly, results from an RCT cannot definitively guide next steps to improve effectiveness, efficiency, economy, or scalability of the intervention. Thus, alternative approaches to intervention development and testing must be considered if investigators want to directly examine the performance of individual or combinations of intervention components.

One such approach is the Multiphase Optimization Strategy. MOST is an engineering-inspired systematic framework for developing, optimizing, and evaluating multicomponent interventions. Optimization is the process of identifying the intervention that produces the best expected outcome given key constraints (see Table 1 for key terms used in MOST).[10–12] Consideration of constraints throughout the development and testing processes increases the likelihood of achieving effectiveness, efficiency, economy, and scalability. MOST comprised three phases preparation, optimization, and evaluation. Each phase within the MOST framework has an overarching objective with key milestones that once reached result in outputs utilized in the next phase or throughout the MOST cycle (Fig. 1). As the objective of each MOST phase differs, the experimental designs commonly used in each phase also differ. In general, the MOST phases follow a general progression with the preparation phase leading to the optimization phase which results in an optimized intervention that is used in the evaluation phase which then is further optimized in additional iterations of this

preparation-optimization-evaluation cycle. This ongoing, iterative process is called the continuous optimization principle. The activities of each phase and iterative flow of the MOST framework is highlighted by Wyrick et al. in their myPlaybook intervention study targeting substance use in college student-athletes.[14] First, the authors highlighted how they developed their conceptual model, identified intervention components to target key concepts in the model, and selected constraints for the optimization criterion during the preparation phase.[14] Wyrick et al. then described an ongoing iterative procedure examining effect size of individual intervention components for inclusion in an optimized intervention during the optimization phase.[14] For the evaluation phase, Wyrick et al. describe a planned RCT comparing the optimized myPlaybook intervention to the original version.[14]

Similar to the RCT and "bundled" intervention approach, in the preparation phase, the investigator develops a theoretically and empirically driven conceptual model that identifies intervention components. The role of this model is twofold: 1) to identify key concepts and relationships on which to intervene and 2) to guide component selection.[10,12,14,20,21] Once components are identified, the investigator conducts any necessary pilot-testing with the purpose of understanding acceptability and feasibility. Of note, a pilot test is hypothesis generating rather than hypothesis testing in the MOST framework,[22] similar to most behavioral intervention pilot studies.[23–25] Finally, in the preparation phase, the investigator identifies the optimization criterion, or the goal of optimization.[10,21] For example, in the Fit2Thrive study protocol, Phillips et al. identified an optimization criterion of the most effective physical activity intervention measured by greatest increase in average physical activity minutes that can be implemented for $550 or less per person.[26] The optimization criterion specifies the constraints that an intervention must consider to achieve the desired qualities of effectiveness, efficiency, economy, and scalability. Identification of the optimization criterion is a key activity within the preparation phase to ensure all necessary data, including those related to cost, time, or other common constraints, are collected during the optimization phase.[10]

In the optimization phase, the hallmark activities are the optimization trial and the identification of the optimized intervention using empirical data. Several experimental designs are appropriate for the optimization trial, but are dependent upon the research question, type of intervention (fixed vs. adaptive), and the resource management principle. The resource management principle requires the investigator to "strive to make the best and most efficient use of available resources when obtaining scientific information."[27] Suitable experimental designs include factorial experiments, fractional factorial experiments, micro-randomized trials, or sequential, multiple assignment, randomized trials. In a factorial experiment, candidate components are operationalized as factors with two or more levels. Levels may be operationalized as on/off (text message reminders vs. none) or differing number of sessions (1 vs. 3 coaching sessions). These levels are then experimentally manipulated to identify the individual effect of each factor on the outcome as well as how the factors interact with one another and the contribution of that interaction toward the outcome of interest. At the conclusion of the optimization trial, the results are used to empirically identify the components and levels that produce the best expected outcome and meet the optimization criterion. Finally, in the third phase of MOST, the evaluation phase, the effect of the optimized intervention from the optimization trial is compared to a suitable

control via an RCT.[10,14,21] Adhering to the resource management principle, if the optimized intervention is not expected to be sufficiently effective, rather than moving to the RCT, it is recommended the investigator return to the preparation phase.

MOST is a framework and should not be considered an experimental design or "off-the-shelf" method. In the MOST framework, an investigator uses an iterative process to develop a multicomponent intervention with four desired qualities: effectiveness, efficiency, economy, and scalability.[10,21] Effectiveness (or efficacy) is the expectation that an intervention will be beneficial in a real-world setting and that the benefits will outweigh the harms. Efficiency is the extent to which an intervention avoids wasting limited resources (e.g., clinician time, clinic space, and costs). Economy is the extent to which an intervention can be executed within the confines of budgetary constraints and offers a good value for the resources used. Scalability is the potential of the intervention to be implemented with fidelity in real-world practices. The MOST phases may be conceptualized as cyclical: the components of an optimized intervention may be continually refined to further optimize the intervention package. Over multiple cycles of optimization, the effectiveness, efficiency, economy, and scalability of an intervention are greatly improved, thereby hastening the progress of translational research and maximizing public health impact.[28] In the following sections, we describe activities within each phase of MOST and highlight the practical considerations to the palliative care field.

Activities and Applications of MOST

Preparation Phase

Role of the Conceptual Model.—Often based on one or more theories derived from empirical literature, conceptual models describe concepts and processes that are hypothesized to causally explain and predict change in the primary outcome of interest. Further, the conceptual model also guides the selection of candidate components, component levels, and measures. Each component is linked to individual concepts and processes in the model (i.e., mediators) to show the purported mechanism by which one expects the components to interact with one another and to effect change on short- and long-term outcomes.

Conceptual models can be effectively conveyed when narrative description is accompanied by a figure that allows readers to readily ascertain the intervention components, the causal factors the components are targeting, and how the components lead to change in the primary outcome. Note, the purpose of the conceptual model is to depict the theory of change for the intervention. For this reason, it is recommended that one component target one mediator. The relationship between components and other mediators can be explored post hoc. Other intervention examples showing conceptual models using the MOST framework can be found in the included citations.[10,12,16,29]

Pilot Testing.—After establishing the conceptual model and identifying the intervention components, a pilot test is often conducted to evaluate feasibility and acceptability of a factorial or other trial design incorporating the selected components and component levels. It may also be desirable to pilot test the experimental design selected for the optimization trial.

This may be useful when the design is new to the team and the acceptability and feasibility of recruitment, retention, randomization, and protocol implementation must be ascertained. Given the aims of feasibility and acceptability, pilot studies are not powered for hypothesis testing and as such, do not function to provide definitive evaluation of component effectiveness. Pilot trials may also include aims examining potential efficacy or mediators or moderators between intervention components and outcomes of interest. One notable difference between the use of factorial trials in the preparation versus the optimization phase is power. A pilot factorial experiment, by definition, is not powered to estimate effects.

Optimization Phase

The overall objective of an optimization trial, the primary activity of the optimization phase, is to identify the optimized intervention. This is achieved via a highly efficient experimental trial in which information about the performance of individual intervention components and their interactions are collected.[8,30,31] Going forward, we provide hypothetical examples assuming a fully powered factorial trial. Research questions of an optimization trial may be related to the main effects or interaction of intervention components. For example, one of the research questions might be to determine the main effects of individual intervention components on patient-reported positive decision influence at 24 weeks. Other secondary research questions may focus on exploratory mediation or moderation analyses.

In the factorial experiment example, candidate components (palliative care coaching, communication training, and decision support training; Table 2) are referred to as factors. The example study has three factors with 2 levels each, representing a $2 \times 2 \times 2$ (i.e. 2^3) factorial experiment. This will produce eight different experimental conditions, or combinations of the factors and factor levels that are being tested. Although one might desire to have more than two levels of a component, 2^k factorial trials allow for the most efficient use of participants (where k represents the number of components) as with increased levels the needed sample size to maintain power often doubles.[32] Levels of factors may be set to off/on (i.e., “include/do not include”) or different levels of intensity (i.e., “high dose/low dose”). In the example, the two levels of the component #1 are a single session (“low dose”) versus three sessions (“high dose”). For both the component #2 and component #3 factors, the levels are a single session versus no sessions.

Estimating Sample Size and Power in a Factorial Experiment.—It is important to highlight at this point that while the 2^3 example trial has eight conditions, it should *not* be perceived as an 8-arm RCT. In a traditional RCT approach, power is related to the per-arm sample size. Factorial designs have small within-condition sample sizes as the overall sample size is an aggregate across all conditions. Evaluation of a particular factor’s two levels includes splitting the total sample size in half and comparing the aggregated means across conditions between the two dosage levels of a single factor.

Therefore, statistical power is based on the comparison between factor levels. Additionally, if interactions between factors will be considered, power must be sufficient to determine the smallest size interaction necessary to guide component inclusion decisions.[10,31] Given this, when one or more additional factors are added to a factorial experiment, the sample size

does not change, the levels do not exceed already included, and no additional higher-level interactions are considered necessary.

General Approach to Data Analysis in Factorial Trials.—Classic factorial general linear modeling conducted with effect coding is a common statistical approach in evaluating factorial trial data, including main effects of each component and interactions between components.[10] Effect coding is recommended as it provides reasonable, uncorrelated main and interaction effect estimates in a model given equal sample size per condition.[33] A component's main effect on an outcome is ascertained by computing the difference between the mean outcome score of one level of the component and the mean score of the other level averaged over all levels of the other components.

Component interactions occur when one level of a factor demonstrates different mean outcome scores depending on the level of one or more other factors. In a two-way interaction, the effect of a factor level varies in the presence of another factor, averaging over all other factors. Higher order interactions are extensions of the above analysis. More detailed guidance and information concerning factorial trial analysis can be found elsewhere.[8,10,33–35]

Identifying the Optimized Intervention.—The empirical results of the optimization trial are used to identify the optimized intervention. This is done through a systematic process of 1) examining important main effects, retaining or "screening in" components that demonstrate a specified effect size, 2) examining interactions, potentially "screening in" components with synergistic interactions and "screening out" components with antagonistic interactions depending on their overall impact, and, if applicable, 3) taking the predetermined constraints of the optimization criterion into account, decide which components at which level will be included.[10,32] Some investigators may specify an all active components optimization criterion during the preparation phase. In the optimization phase, components are kept or "screened-in" if they demonstrate a large enough effect size in the desired direction and set to the level associated with best outcome. With the all active components optimization criterion, there are no predetermined constraints that will be considered in the identification of the optimized intervention.

Note, this decision-making or "effectiveness" criterion is different from an optimization criterion. The optimization criterion further evaluates the "screened in" set given the context of effectiveness, efficiency, economy, and scalability.

Given an all active component optimization criterion, no further decisions for retaining components may be needed beyond sorting into the "screened in" set. If the study included an optimization criterion of the greatest improvement in positive decision influence that costs $300 or less to deliver per person, additional decisions regarding retained components will ensue. For example using Table 2, if the high levels of component #1 (3 sessions) and component #2 (1 session) cost over $300 to implement, combinations of components that exceed the cost constraint are ruled out. Additionally, in the absence of a detectable difference between levels, the lower level is retained which may mean excluding a component.

Evaluation Phase

If the optimized intervention identified in the optimization phase is expected to be effective, it is then evaluated in an RCT against a suitable control. This RCT could provide important information for clinical practice moving forward. However, recall the continual optimization principle. This suggests that even an optimized intervention can be further optimized as there are always new constraints or scientific advancements to consider.

Discussion

The purpose of this paper has been to provide a general overview of MOST. MOST can be used to optimize multicomponent interventions across the entire palliative and hospice care spectrum and other research fields. The factorial experiment methods discussed in this paper as part of the optimization phase of MOST are not novel per se; however, to the best of our knowledge, there has been little use of the factorial trial design, and MOST, in palliative care intervention development and testing. Given the need for future palliative care interventions to show what components are "active" and beneficial in improving patient and family outcomes, we believe the MOST framework and factorial experimental design is critical for the field of palliative care. Our team is conducting a pilot 2^3 factorial trial entitled CASCADE (Care Supporters Coached to be Adept Decision Partners) to develop and test components of an early palliative care intervention (effective social support psychoeducation,[36,37] communication training, and Ottawa Decision Guide training[38–40]) to train advanced cancer family caregivers in how to partner with patients when facing treatment and other health-related decisions. Further details of Project CASCADE can be found on ClinicalTrials.gov (NCT03947606). Based on our experiences with the MOST framework and the factorial trial design, we provide some further considerations for researchers interested in this approach.

Several considerations merit highlighting regarding the actual conduct of a factorial trial. First, a factorial trial is randomizing participants to multiple conditions, which might include 8, 16, 32 or even more experimental conditions. The underlying principle of randomization to groups remains the same as a 2-arm RCT, however, and randomization blocking should be configured to allow equal numbers of participants for each experimental condition.[41] It is not uncommon for there to be imbalances in participant characteristics, attrition, and missing data between individual conditions. While investigators might want to evaluate individual conditions for feasibility issues that may contribute to attrition, main effect analyses are generally robust to these imbalances because conditions and their samples are pooled when examining the two levels of a single factor.[8,11]

Second, a factorial trial has many more experimental conditions than a traditional RCT and hence additional strategies need to be employed to keep participants in the condition to which they are assigned to minimize contamination and protocol deviations. For CASCADE, we have employed several strategies to maintain fidelity consistent with National Institutes of Health and TIDieR guidelines.[42,43] This includes having separate CASCADE Toolkits, interventionist scripts, and interventionist charting templates for each individual condition. In addition, all sessions are audio-recorded and reviewed with a fidelity checklist by study staff (RDW). Coaches also receive standardized training and meet weekly

with the Principal Investigator and other co-investigators for clinical supervision in part to ensure participants are receiving the correct CASCADE components for their assigned condition. Additional guidance and strategies to maintain fidelity to assigned conditions in a factorial trial is discussed by Piper and colleagues.[44]

Third, when designing a factorial trial, it is important to consider the participant's experience with the trial design.[44] While factorial trials are more complex than traditional RCTs, participants do not necessarily need to understand the fine details of the charting, data collection, and fidelity strategies that are intended to track eight or more different conditions. For CASCADE when we initially approach potential participants for informed consent, we briefly describe the different components of CASCADE they might receive, including risks. Participants are informed that they will receive anywhere from 1 to 5 CASCADE sessions depending on the group to which they are randomly assigned. Once randomized, participants receive a letter and flyer that summarizes exactly which CASCADE components they are receiving.

Conclusion

It is imperative that the specialty of palliative and hospice care expand its toolkit of clinical trial designs to advance interventions in serious illness and end of life. There is a need for interventions that are not only effective, but also efficient, economical, and scalable. A key innovation has been the MOST framework which uses the factorial experiment and other highly efficient designs to test the individual components of multicomponent interventions and to understand the relationships between components. This trial design, now in use for over a decade in other areas of behavioral research, has the potential to greatly expand the universe of potential palliative care interventions and enhance the speed and efficiency of their production.

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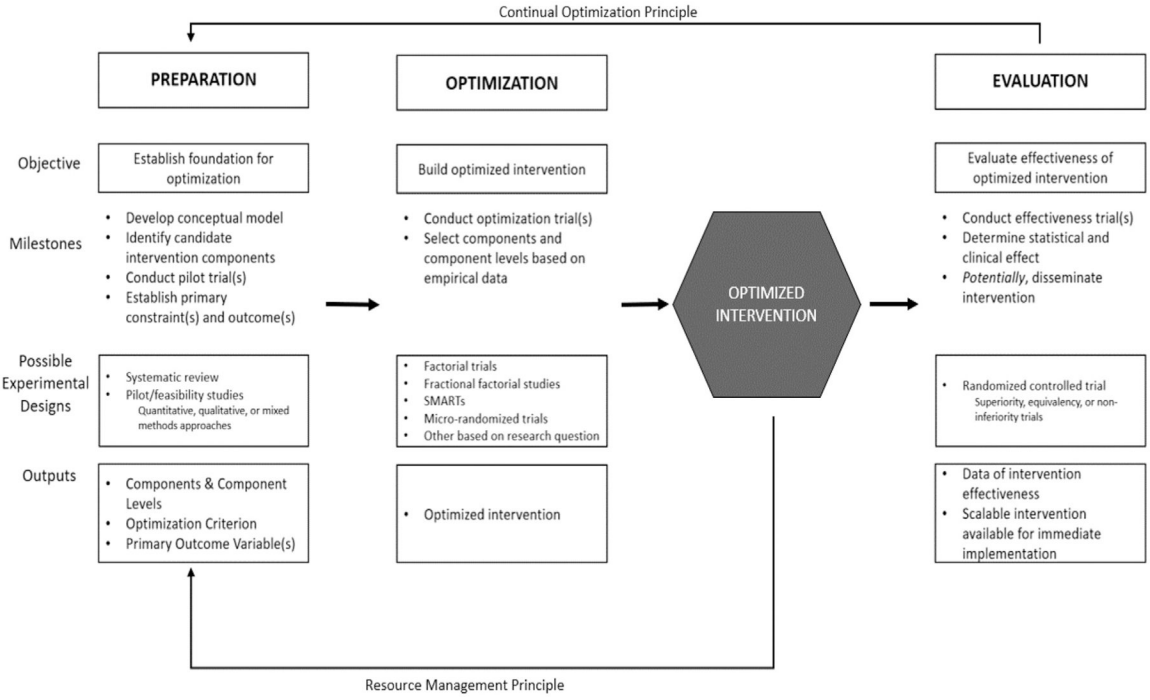

Fig. 1.
Phases of the MOST framework.

Table 1

Select Key Terms Used in the Multiphase Optimization Strategy (MOST) and Factorial Trial Design

Term	Definition
Component	Any part of an intervention that can be separated out for study
Continual optimization principle	A guiding axiom in MOST where optimization is an iterative process toward a continuously improved intervention
Constraint	A restriction (time, money, participant burden, personnel, equipment, or other resources) that may limit the implementation of the intervention
Economy	Management or extent to which an intervention produces positive outcomes and is implemented without exceeding resource budget (money, time, or other health-care services/products)
Effectiveness	Determination that a treatment overall improves outcomes within a real-world setting
Efficiency	Extent to which the intervention improves outcomes with judicious use of health-care resources
Evaluation	Stage of the MOST framework following Optimization which aims to evaluate the effectiveness of the optimization intervention through an RCT
Factor	Independent variable in a factorial trial
Factorial experiments	An experimental design where the investigator manipulates factors (in MOST, intervention components) with differing levels at the same time resulting in multiple experimental conditions allowing for evaluation of main and interaction effects
Level	A discrete amount or presence of a factor in a factorial trial, often notated as a quantity (# of sessions) or presence/absence of an intervention element (Yes vs No text message reminders)
Multiphase Optimization Strategy (MOST)	A framework for preparing, optimizing, and evaluating multicomponent interventions making the best use of available resources. MOST is *not* a clinical trial design
Optimization	The process of identifying a multicomponent behavioral or biobehavioral intervention that provides the best expected outcome obtainable within key constraints imposed by the need for effectiveness, efficiency, economy, and/or scalability
Optimization criterion	A function of best expected outcome and key constraints (time, money, participant burden, and so forth) used to selection of intervention components and levels for inclusion in the optimized intervention
Resource management principle	A guiding axiom in MOST stipulating that investigators effectively and efficiently balance available resources in quest for scientific information
Scalability	The extent to which an evaluated, optimized intervention can be implemented without adjustment

Table 2

An Example 2^3 Factorial Trial Design for a Palliative Care Intervention

Condition	Component #1	Component #2	Component #3
1	1 session	1 session	1 session
2	1 session	1 session	No session
3	1 session	No session	1 session
4	1 session	No session	No session
5	3 sessions	1 session	1 session
6	3 sessions	1 session	No session
7	3 sessions	No session	1 session
8	3 sessions	No session	No session

This factorial design should not be considered an 8-arm trial in which 7 conditions are compared to a control condition.