

Standardly-Tailored Multicomponent Interventions Trial Designs For Multifactorial Health
Syndromes: An Example From Geriatrics

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Abstract:

Many clinical trials are designed to test an intervention arm that receives a single therapeutic agent against a control arm that uses the standard therapy or a placebo. However, many common and morbid health problems, particularly in older persons, have a multifactorial etiology. Geriatric syndromes such as falls, delirium, and the development of disability in activities of daily living, for example, are known to result from variable combinations of risk factors. In fact, many health conditions have multifactorial etiologies, including cardiovascular, depression and numerous chronic diseases. Multifactorial syndromes are defined as health conditions in which more than one risk factor is related to the outcome. Hence, a newer type of design called a standardly-tailored multicomponent interventions trial is being used to modify risk factors and thus, reduce the frequency of adverse health outcomes.

Standardly-tailored designs assign components of a multicomponent intervention based on *a priori* risk factor assessment based on protocols linking the results of risk factors assessments to the recommended intervention components. While standardly-tailored designs are clinically relevant and yield an estimate for the overall intervention effect, previous applications of these designs have not provided unbiased estimates of individual component effects because components often target several risk factors and may be confounded. Therefore, guidelines for the design of standardly-tailored multicomponent intervention trials, whether in geriatrics or other areas of medical research need to be developed. Therefore, in this proceeding, we address some key statistical and clinical issues related to the design of standardly-tailored trials of multicomponent interventions for multifactorial health conditions and potential methods to estimate intervention component effects.

Introduction

In an earlier article we discussed issues related to the design of clinical trials to test multicomponent interventions for multifactorial health conditions (Allore et al., 2005).

Multicomponent interventions of multifactorial geriatric health syndromes commonly assign individual components of the intervention based on *a priori* risk factor assessment. This type of intervention component assignment is called standardly tailored. While standardly-tailored designs are clinically relevant and yield an estimate for the overall intervention effect (Allore et al., 2005) it is not known if individual component effects can be unbiasedly estimated.

Estimating intervention component effects could reduce the number of intervention components that should be applied in clinical practice.

While a multicomponent intervention approach is reasonable because of the multifactorial etiology, the design and analysis of such trials are complicated. Some clinical investigators have been disinclined to design and test multicomponent interventions, both because of their greater intricacy and because of the concern that it is not possible to separate the effects of the individual components to decide those that are beneficial. Because of this reluctance, many potentially effective multicomponent interventions have been left untested. Because each component of an intervention adds to the overall cost and complexity, being able to directly estimate component effects could greatly enhance efficiency by reducing the number of components introduced into clinical practice.

In this article, we present some fundamental statistical and clinical issues related to the design of standardly-tailored trials of multicomponent interventions for multifactorial health conditions in geriatrics and discuss approaches for estimating unbiased component effects.

Example of Multifactorial Geriatric Syndromes: Injurious Falls

An example of a multifactorial geriatric syndrome where standardly-tailored multicomponent intervention trials have been conducted is injurious falls in the elderly (Tinetti et al, 1994, Shaw et al. 2003, van Haastregt et al. 2003, Jensen et al. 2003). Risk factors that have been shown to increase the risk of falling or fall injuries include depressive symptoms, postural hypotension, impairments in cognition, vision, balance, gait, or muscle strength, and

the use of four or more prescription medications. The risk of falling increases as the number of these risk factors increases. While modifying only one of these risk factors may reduce the incidence of falls, the risk reduction is likely to be greater when several risk factors are modified (i.e. treated). The Cochran review (Gillespie et al., 2004), using data from nine trials, found that the single component intervention of untargeted exercise/physical therapy had a pooled risk ratio of 0.89 while four trials of multidisciplinary, multicomponent health/environmental interventions showed a pooled risk ratio of 0.73. A review and meta-analysis of 40 fall prevention trials (Chang et al, 2004); found that no trial directly estimated individual component effects. In their meta-regression analysis, multifactorial risk assessment and management was associated with an adjusted risk ratio of 0.82 for falling at least once, but the different effects of each exercise could not be estimated.

Concerns Related to Standardly Tailored Trials

In designing multicomponent interventions both clinical and statistical issues arise that make these trials more complicated. These issues are briefly outlined in Table 1 and are presented in more detail in Allore et al. (2005).

In the traditional randomized clinical trial (RCT), the intervention components and their level (such as, frequency of exercise, dose of drug) are assigned to the participant and all participants are eligible for all components. However with multifactorial geriatric health syndromes, participants have one or more modifiable risk factors at enrollment, but rarely do all participants have all risk factors. Consequently, investigators do not randomly assign standardly-tailored components to participants in the same way as they might in a traditional full factorial RCT. Rather, the option for those randomized to the intervention arms is to apply each intervention component to each modifiable risk factor present at the time of enrollment.

Randomization

Clinical trials use randomization to control for both measured and unmeasured factors that have an effect on the treatment comparison. The level at which randomization can occur varies from the participant to a cluster or group (i.e. physician, ward, or site) level. For a standardly-tailored design, a participant would be randomized to the intervention or control arm, and those in the intervention arm would receive the intervention component for each risk factor they had. An important consideration is that the control arm must have the same balance of risk factors as the intervention arms. Thus, stratified randomization based on stratification of risk factors present may be the preferable form of randomization. Challenges arise when clusters are the unit of randomization, but these are beyond the scope of this article.

Methods to Estimate Individual Intervention Component Effects

The most intuitive approach to estimating multiple components simultaneously is a full factorial design. Full factorial designs have been applied in the agricultural and industrial setting for over half a century (Plackett, 1946; Cochran and Cox 1957). However, this design has been used less frequently in medical trials where only a few components were studied simultaneously (Byar and Piantadois, 1985; Li, 1993; Donta et al., 2003, Apfel et al., 2003). For example, in the Donta et al. (2003) RCT of Gulf War veterans' illness two therapies, cognitive behavioral therapy and aerobic exercise, were evaluated in a 2x2 factorial design.

A major issue in estimating individual component effects is determining the appropriate comparison group. For example, if a single component effect were to be estimated in a standardly-tailored design, the appropriate comparison group would be participants in the control arm who have the risk factors that would have made them candidates to receive that component. This comparison group is different from one consisting of all participants who did not receive the component because some participants who did not have the risk factor in the control group would not be candidates for the component.

Limitations of Full Factorial Designs for Multifactorial Syndromes

Traditionally, RCTs test intervention components that all subjects can potentially receive. For example, if two intervention components A and B are to be studied, design options include: 1) three 2-arms trials (A vs. control, B vs. control and A+B vs. control), 2) a single 3-arm trial (A vs. B vs. control), and 3) a 2x2 factorial design (A alone, B alone, A+B, and neither treatment). Factorial designs are efficient to detect marginal effects in the presence of no interaction. To detect internal effects in a factorial design makes it equivalent to a 4-arm trial. Differences between these designs include the number of participants needed to have the same precision in effect estimates and whether or not interactions can be estimated (Wu and Hamada, 2000). Furthermore, for option 1, since the intervention components effects are estimated separately (e.g. A vs. control and B vs. control), comparisons among components cannot be made. For option 2, the intervention component estimates are not independent because they are based on the same comparison group. In contrast, for the full factorial design the intervention component effects are independent and both main effects and interactions can be estimated. Full factorial designs also have the reproducibility property (Fisher, 1971), thus, they have a wider inductive basis for inference about treatment effects.

A problem with full factorial designs is that sample size grows geometrically as factors are added. For example, to study four binary risk factors, the number of treatment arms would be $2^4 = 16$. Additionally, the full factorial design requires that each participant is eligible to be randomized to any treatment arm. Thus, for multifactorial geriatric health syndromes all potential participants would need to have the same set of risk factors to be eligible for the trial. That is, eligible participants for full factorial trials must have all of the risk factors to be modified and, thus, the design cannot be standardly-tailored. Furthermore, full factorial designs may be inappropriate for certain clinical trials in which several intervention strategies or components are provided to participants as a package and some components are known *a priori* to have a qualitative interaction or are contraindicated for some participants (Byar et al., 1993). Moreover,

in a medical setting, the management of a large number of unique component combinations would be logistically impractical or infeasible (Byar, 1990a).

Fractional Factorial Designs

One possible approach to the problem when there are a large number of components of an intervention is to consider a fractional factorial design (Plackett 1946, Cochran and Cox 1957). This type of design has been advocated (Byar 1990a, Stolle 2002) but has been rarely used in medical trials (Li et al., 1993; Burns et al., 1997). A fractional factorial design is one in which only a fraction of the treatment combinations required for the complete factorial experiment is used. The fraction of the treatment combinations is chosen by selecting one or more defining contrasts (Fleiss, 1999), resulting in some effects being orthogonal (or unconfounded) and the remaining effects confounded (Cochran and Cox 1957). Confounded effects cannot be estimated separately or distinguished from one another because the values for the levels of each involved term in the design matrix are identical. For example, use Inouye trial. Typically, higher-order interactions are chosen to be confounded and main effects and possibly two-way interactions are chosen to be unconfounded. The resolution of a design indicates the highest order of interaction that is not confounded with other interactions of the same order (Cochran and Cox, 1957). For example, in a resolution III design the main effects can be estimated but interactions are confounded. Fractional factorials designs must be planned to have a defining contrast because such contrasts are unlikely to arise by chance allocation of treatments. When there is not *a priori* allocation to treatment arms, an inefficient, unbalanced trial can result, leading to biased effect estimates and the inability to measure some or all main effects or interactions of interest.

An example of a 1/2 fractional factorial resolution III design for an intervention to prevent nursing home acquired pneumonia is provided in Table 2. This design is based on three factors that were found to be risk factors for nursing home acquired pneumonia in an observation study

by Quagliarello, et al. 2005 – lack of vaccination, oral care and swallowing therapy. The design allows for unbiased estimation of all three main effects with only four treatment arms compared with eight treatment arms needed for a full factorial design, i.e., 2^3 ; however, all higher order interactions are confounded. Again, fractional factorial designs assume that all participants are eligible for all treatment arms and, thus, have all the risk factors that the intervention component is designed to modify.

Incomplete Factorial and Modified Reciprocal Control Designs

There is a variant of the factorial design called the incomplete factorial design (Byar et al., 1993) that specifically addresses effect estimation when there are ethical considerations or problematic component combinations. For example, if the multicomponent intervention had three components that were each different medications, as is common in HIV/AIDS trials, it may be considered toxic to have a treatment arm where participants received all three medications. Thus, this specific treatment arm would be eliminated from the design. The problem with this design is that best linear unbiased estimators (minimum mean squared error) cannot be obtained (Byar et al., 1993). However, variances, covariances and bias can be estimated (McLean and Sanders, 1988; Byar et al., 1993). Another variant that could be considered is a modified reciprocal control design, where some participants serve as both a measure for some intervention components and controls for others. That is, a participant with three modifiable risk factors may be randomized to receive intervention components for two of their three modifiable risk factors and serve as a control for the effect estimate of the third modifiable risk factor (Byar, 1990b, Green and Freedman, 1994).

Conclusion

Because there are many medical syndromes that are multifactorial and can only be effectively treated by modifying many risk factors, standardly-tailored designs are being applied

to evaluate multicomponent interventions. Areas for future research and specific questions that need to be addressed to successfully apply standardly tailored designs are outlined in Table 3. Additional research is needed to establish guidelines for determining how to group modifiable risk factors to reduce the number of factors, as well as for assigning components of an intervention, such as the reciprocal control design. Practical matters, such as, sample size calculations need to be extended to component effect estimation and analytic models need to be developed to provide unbiased component effects. Answers to these questions would aid in the design of efficient multicomponent intervention trials of multifactorial geriatric and other types of medical syndromes.

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Table 1. Statistical and clinical considerations in the design of standardly tailored multicomponent intervention trials (modified from Allore et al (2005)).

Issue	Statistical consideration	Clinical consideration
Prevalence of risk factors	Low prevalence increases the number of participants that must be screened to find eligible participants and makes it harder to estimate component effects.	Prevalence of medically important risk factors may be low, but some are amenable to intervention and have high risks associated with them.
Correlation among risk factors	Results in unreliable effect estimates and increased variability. Most statistical models assume independence of predictors.	Many important risk factors are likely to be correlated in geriatric syndromes.
Grouping of risk factors	Grouping may reduce the correlation among and increase the prevalence of risk factor groups, thereby enhancing the estimation of component effects.	Groups must make clinical sense. It is not always apparent how to group risk factors. Within a grouping, some risk factors may respond to an intervention and others not; limiting our ability to translate results into practice
Number of intervention components	Increasing the number of components will likely increase the sample size required to test component effects.	Observational studies have found numerous risk factors for geriatric outcomes. Increasing the number of components to reduce risk factors effects could lead to the greatest reduction in negative outcomes.
Measurement of predetermine risk factors at follow-up	Will provide information about the extent to which a risk factor has been modified and which components affected modification. However, unbiased assessment of risk factor modification will be difficult because of correlation.	Adds to the cost and labor of conducting a trial. There may not be a readily available measure of the risk factor that is sensitive to change.
Eligibility	Restrictive criteria will affect generalizability and possibly sharpen treatment comparisons; broad criteria will impact on enrollment and possibly dilute treatment effects.	Hypothesis may be specific to a group of people with a given condition. Need to know to whom results are generalizable.

Blinding	Controls for selection and measurement bias. Double-blinding is preferred but rarely applicable as most interventions modify behavior or environment. However, single-blinding of the interventionist to the allocation to intervention or control arms and outcome assessment should be performed	May not be possible to blind participants to their assignment to the intervention arm because of behavioral or environmental components.
Assignment of components	Clear assignment of intervention components to risk factor groups is required to measure individual component effects.	Components may modify more than one risk factor. Assignment depends on whether the participant has the risk factor.
Sample size	Few methods exist besides ANOVA for estimating sample sizes for multiple comparison groups. Adjusting for clustering has not been developed for multicomponent intervention trials.	Increasing sample size adds to the cost of the intervention trial.
Estimating individual component effects	The major issues include the selection of an appropriate comparison group and obtaining unbiased component estimates when individuals do not receive all components of the intervention or have all risk factors. This problem is further complicated if a clustered design is used.	Multifactorial geriatric syndromes are best treated with multicomponent interventions. Thus, methods need to be developed to analyze intervention trial results to reduce the cost and burden of applying the intervention in the field.

Table 2 Design matrix for a 1/2 fractional factorial of resolution III for 3 components of a multifactorial intervention to prevent nursing home acquired pneumonia. -1 denotes that the component is absent and 1 denotes that the component is present.

Treatment combination	Components of the intervention		
	Vaccination	Oral Care	Swallowing Therapy
1	-1	-1	1
2	1	-1	-1
3	-1	1	-1
4	1	1	1

The defining contrast is: swallow = vaccination X oral care.

Table 3 Areas for future research in standardly tailored designs. (Modified from Allore et al. (2005))

Areas for Research	Unanswered Questions and Issues
Reporting of multicomponent intervention trials	Develop a common terminology for the elements of multicomponent intervention trials. Develop reporting standards.
Study Design	Can incomplete factorial or reciprocal control designs be applied to multifactorial syndromes and what are their limitations?
Selection of modifiable risk factors	How many risk factors can be studied in a single trial? What is the minimum prevalence of a risk factor? What is an acceptable level of correlation among risk factors? How can risk factors be grouped?
Selection and assignment of intervention components	How many components can be studied in a trial? How to determine which risk factors an intervention may affect? By how much does a component need to reduce the risk of the targeted risk factor to be effective?
Sample size determination	How to determine the sample size needed to estimate component effects for given designs?
Estimation of component effects	What is the appropriate comparison group? What methods will provide unbiased estimates of individual component effects?

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