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Using the SAS® System for Experimental Designs for Multicomponent Interventions in Medicine

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ABSTRACT

We demonstrate how to use SAS® to design experiments for multicomponent interventions for multifactorial health syndromes. Multifactorial syndromes are health conditions that have more than one risk factor related to the outcome and require interventions with several components that target different risk factors. The design and analysis of multicomponent trials are complicated by the number of factors to be studied and the interdependency among the factors. A full factorial design is appropriate when there are a few risk factors to treat; however, when there are many risk factors to treat, fractional factorial designs allow for estimation of the main effects at the sacrifice of higher-order interactions (available in ADX Interface SAS/QC® software). When selecting risk factors to treat, researchers must consider the inter-relationships among factors, particularly interactions (using ADX). Randomization to treatment arms needs to consider whether participants can be individually randomized (the PLAN procedure) or if the trial design requires the use of cluster randomization (the SURVEYSELECT procedure). Clinical investigators have been reluctant to design and test multicomponent interventions, both because of their greater complexity and of the concern that it is not possible to disentangle the effects of the individual components to determine those that are beneficial. Because of this reluctance many potentially effective multicomponent intervention strategies have been left untested. Furthermore, each component of an intervention adds to its overall cost and complexity; thus, designs that allow estimation of component effects could greatly enhance efficiency. The SAS® System has a strong set of tools to help design multifactorial trials.

INTRODUCTION

Multifactorial geriatric syndromes are health conditions in which more than one factor is related to the outcome. For example, several factors that have been known to independently or jointly increase the risk of falling include arthritis, depressive symptoms, orthostasis, and impairments in cognition, vision, balance, gait, or muscle strength. To treat these health conditions, clinicians have developed interventions with multiple components where each component targets one or more different risk factors (Allore et al., 2005). For example to prevent falls, physical interventions have been developed to improve balance, gait or muscle strength (Tinetti et al., 1994). The design of studies to evaluate the efficacy of multicomponent interventions typically involves evaluating the overall effect of the interventions and not the effects of any one component (Gillespie et al. 2004) In such experiments being able to directly estimate component effects is often also important so that the most effective components could be ultimately applied in clinical practice.

Factorial designs traditionally have been used to assess the effect of interventions given singly or in combination. For example, an intervention with components A and B could be designed as a 2x2 factorial with four possible treatment assignments, A alone, B alone, both or neither. However, when there are many components to an intervention, each component adds to the cost and complexity of a clinical trial. Thus, use of full factorial designs may not be feasible and alternative methods, such as fractional factorial designs, need to be considered. Another issue in studies of multifactorial geriatric health conditions is determining which risk factors to intervene upon. Thus, evaluating the interdependence among risk factors is another important consideration.

In this paper, we use readily available methods in SAS to evaluate multicomponent interventions using examples from geriatric research.

FACTORIAL DESIGNS

The most intuitive approach to studying multiple components is to vary each component of interest one at a time in a full factorial design. This design has been used in medicine to evaluate two treatments in a 2x2 design, but has rarely been used to study more than two treatments for practical and power considerations. In factorial designs the sample size grows geometrically as factors are added. For example, to study four binary factors the number of treatment arms would be 2^4 or 16. Practically, this approach may be inappropriate for clinical studies because some combinations of components are known *a priori* to have a qualitative interaction or to be contraindicated (Byar, 1993). Furthermore, in a medical setting the management of a large number of unique component combinations would be logistically impractical or impossible (Byar, 1990a; Stolle et al., 2002).

FRACTIONAL FACTORIAL DESIGNS

One possible solution to studying interventions with many components is to use fractional factorial designs. These types of designs have been advocated (Byar, 1990b; Stolle et al., 2002) but infrequently used. A fractional factorial design is a factorial design in which only a fraction of the treatment combinations required for the complete factorial experiment is used. The ADX Interface in SAS/QC® aids in the creation and analysis of more complex types of designs, such as fractional factorial and response surfaces. The fraction of the treatment combinations is chosen by selecting one or more defining contrasts, resulting in some of the effects being orthogonal and the remaining confounded (Cochran and Cox 1957). Confounded effects cannot be estimated separately, that is, terms are confounded when the levels they take in the design matrix are identical, so that they cannot be distinguished. Typically, higher order interactions are chosen to be confounded and main effects and possibly two-way interactions are chosen to be not confounded. 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).

Fractional factorial designs must be planned to have a defining contrast because such contrasts are unlikely to arise by haphazard allocation of treatments. When there is not *a priori* allocation to treatment arms, an inefficient, unbalanced trial can result yielding biased effect estimates and the inability to measure some or all main effects or interactions of interest. For example, in a delirium prevention trial (Inouye et al., 1999) designed to test an intervention with seven components, all intervention arm participants received the same three components (orientation, therapeutic activities, early mobilization) and then received additional components based on existing modifiable risk factors. Thus, the overall intervention effect could be estimated but individual component effects could not be estimated because orientation, therapeutic activities and early mobilization were confounded. Moreover, by chance or by complete overlap in presence of two risk factors, all participants who received the sleep-enhancement component also received hydration, resulting in further confounding. An example of ADX Interface output to redesign this trial using a 1/16 fractional factorial resolution 3 design is provided in Table 1. This design uses the seven intervention components in the original study, but allows for unbiased estimation of all seven main effects with only eight treatment arms as opposed to 128 treatment arms needed for a full factorial; however, all higher order interactions are confounded. The defining contrasts for this design are sleep-enhancement = orientation*therapeutic activities, vision= orientation*early mobilization, hearing = therapeutic activities* early mobilization, and dehydration = orientation* therapeutic activities* early mobilization.

Table 1 Design matrix for a 1/16 fractional factorial of resolution III for 7 components of a multifactorial intervention based upon Project Recovery (Inouye et al., 1999). -1 denotes that the component is absent and 1 denotes that the component is present. Confounding rules for the contrasts are shown.

Coded Design

	ORIENT	THER_ACT	MOBIL	SLEEP	VISION	HEARING	DEHYDRAT
1	-1	-1	-1	1	1	1	-1
2	1	-1	-1	-1	-1	1	1
3	-1	1	-1	-1	1	-1	1
4	1	1	-1	1	-1	-1	-1
5	-1	-1	1	1	-1	-1	1
6	1	-1	1	-1	1	-1	-1
7	-1	1	1	-1	-1	1	-1
8	1	1	1	1	1	1	1

Principal: ++++

```
SLEEP =  ORIENT*THER_ACT
VISION =  ORIENT*MOBIL
HEARING =  THER_ACT*MOBIL
DEHYDRAT =  ORIENT*THER_ACT*MOBIL
```

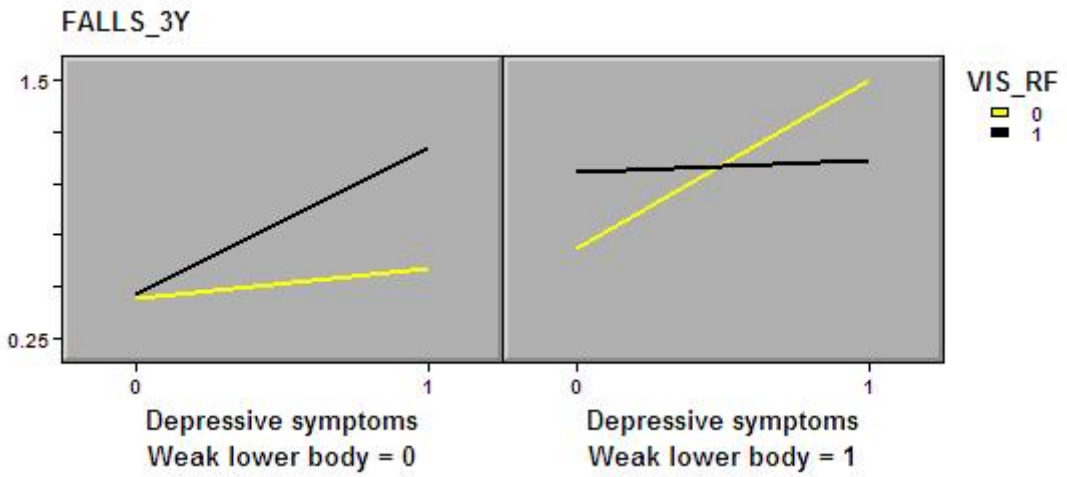
Thus, the ADX Interface in SAS/QC aids in the design and analysis of both full and fractional factorial designs by allowing the user to select the defining contrast(s) by aliasing.

INTERDEPENDENCE AMONG PREDICTORS

An important consideration in the experimental design of studies of multicomponent interventions is determining which risk factors to intervene upon. Because a component can target several modifiable risk factors, determining the interdependence among risk factors is a key factor in the design of such studies. Although the CORR procedure can provide insight into the correlation among risk factors, SAS provides several more insightful methods for determining the inter-independence among risk factors through its ADX interface in SAS/QC.

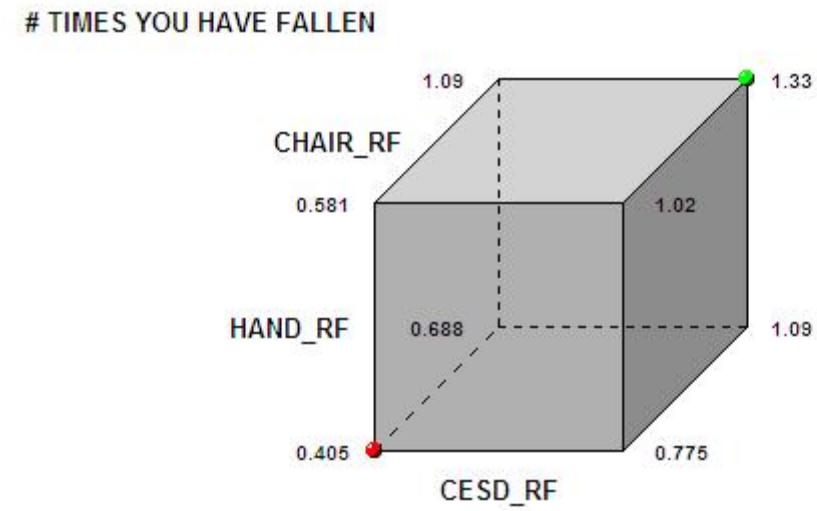
The interaction plot function in ADX interface in SAS/QC is one method that can be used to uncover interactions among risk factors, especially at the planning phase when pilot data are available. We illustrate the concepts using data from Project Safety (Tinetti et al., 1993), a study of the relationship between risk factors and falls in community-living elderly participants. ADX interaction plots that show parallel lines indicate no interaction and demonstrate that if both risk factors are intervened upon, outcome will be improved (data not shown). When the slope of one line is much greater than the other, but the lines do not cross, a quantitative interaction is present (Figure 1 left panel) and indicates that participants with only depressive symptoms may not benefit as much as those with both vision impairment and depressive symptoms. When the lines cross there is a qualitative interaction (Figure 1 right panel) indicating that participants with a weak lower body and vision impairment might not experience a reduction in their number of falls if depressive symptoms were reduced; however, those without vision impairment and but with a weak lower body may experience fewer falls if their depressive symptoms were reduced. Because it is unethical to increase the risk of an adverse outcome, it is important to have as much information as possible about whether reducing a risk factor affects the probability of the outcome in the presence or absence of each other potentially modifiable risk factor. Therefore, information about interactions helps investigators plan which component combinations can ethically be studied.

Figure 1 ADX Interface interaction plot showing a quantitative interaction between the relationship of depressive symptoms and poor vision on falls when there is no lower body weakness (left panel) and a qualitative interaction when there is a risk factor for lower body weakness (right panel). The black line represents the presence of the risk factor for poor vision (VIS_RF=1) and the yellow line the absence of poor vision (VIS_RF=0). The data is from Project Safety (Tinetti et al., 1993) with risk factors measured at baseline. Risk factors displayed are lower extremity function (defined as time required to stand and sit three times > 14 seconds) denoted by "Weak lower body=1", Center for Epidemiologic Studies-Depression-Scale >15 (Radloff, 1977) denoted by "Depressive symptoms=1", and corrected percentage of near visual acuity impairment > 26% (Spaeth, 1955) denoted by "VIS_RF=1". The number of falls is denoted by the variable FALLS_3Y.



Additional features of ADX include cube plots that are illustrated using the Project Safety data in Figure 2.

Figure 2 ADX interface cube plot using Project Safety data showing that the number of falls is minimized (0.405) when all risk factors are absent and the number of falls is greatest (1.33) when all risk factors are present. See text for definitions of variables.



The cube plot informs us that the fewest number of falls occurs when there are no risk factors for upper extremity function (defined as timed signature and denoted as HAND_RF), depressive symptoms (defined as fewer than 16 depressive symptoms from the Center for Epidemiologic Studies-Depression-Scale (Radloff, 1977) and denoted by CESD_RF), and lower extremity function (defined as time required to stand and sit three times denoted as CHAIR_RF). In contrast, the greatest number of falls occurs when all three risk factors are present. The plot also indicates that all interactions are quantitative. Thus, these types of plots are useful for uncovering quantitative and qualitative interactions that would need to be considered in the study design and eventual analysis. However, given that intervention studies usually are not powered to detect interactions (Fleiss, 1986), it is important to have as much information as possible about whether reducing a risk factor affects the probability of the outcome in the presence or absence of other potentially modifiable risk factors. Such information should help investigators determine which risk factor combinations are most likely amenable to intervention. For example, lower cognition may limit the reduction in

falls even though the modifiable risk factors were successfully treated (Jensen et al., 2003). Thus, *a priori* interactions should be specified, so that the study can be suitably designed and powered to measure them.

RANDOMIZATION

Clinical trials use randomization to assign treatments to individual participants or to groups or clusters of participants, e.g., physician, ward or site. Randomization is done because it protects against selection bias, assures balance on both measured and unmeasured factors that can affect the treatment comparison, and assures the validity of most statistical tests. PROC PLAN can be used to construct designs and randomization plans for factorial experiments, especially nested and crossed experiments, and randomized block designs. We illustrate a design with 4 senior housing units to be selected in random order, in which a random permutation of 8 persons will be selected and assigned one of the 8 multicomponent treatments by random permutation.

```
proc plan seed=111605;
      factors  Senior_Housing= 4 person=8;
      treatments treat=8 cyclic (1 2 3 4 5 6 7 8);
run;
```

The output for this design is displayed below, where senior housing unit number 3 is first approached and the seventh enrolled person receives multicomponent treatment number 1.

Senior_ Housing	-----person----	-----treat-----
3	7 4 2 6 5 3 1 8	1 2 3 4 5 6 7 8
2	1 5 3 4 7 6 8 2	2 3 4 5 6 7 8 1
4	3 6 2 1 8 7 5 4	3 4 5 6 7 8 1 2
1	1 6 7 2 5 3 4 8	4 5 6 7 8 1 2 3

For complex sampling, PROC SURVEYSELECT offers a variety of ways to perform probability-based random sampling. For example, consider a sampling frame of senior housing residences of two types (public or private) and three sizes (small, medium or large) where the probability of being sampled is to be proportional to size. The following code can be used to select two senior housing residences per strata of Type and Size under this design:

```
proc surveyselect data=SeniorHousingFrame
         method=pps_brewer
         seed=120705 out=SampleSeniorHousing;
      size NumResidents;
      strata Type Size;
run;
```

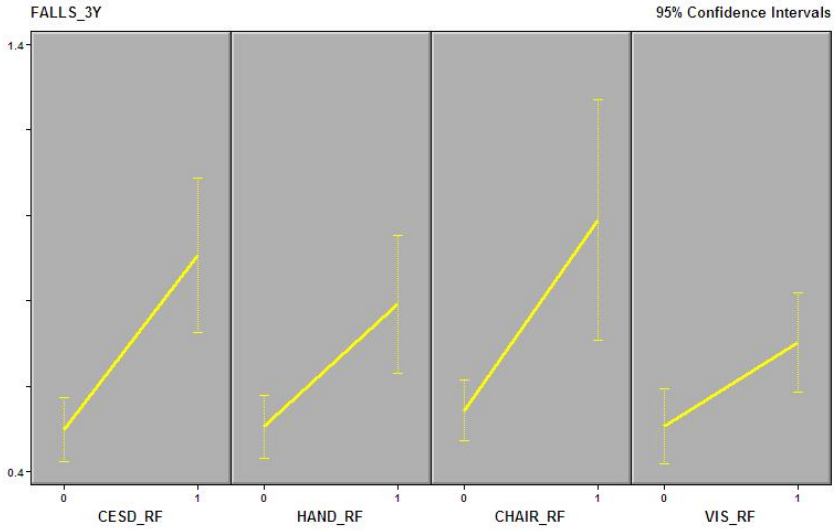
The output is as follows, where for each type of senior residence, two are selected in each size category.

Obs	Type	Size	ID_Senior Residence	Num Residents	Selection Prob	Sampling Weight
1	Private	Large	218	231	0.35566	2.81169
2	Private	Large	241	231	0.35566	2.81169
3	Private	Medium	062	76	0.27993	3.57237
4	Private	Medium	227	70	0.25783	3.87857
5	Private	Small	124	33	0.16058	6.22727
6	Private	Small	116	49	0.23844	4.19388
7	Public	Large	236	279	0.33254	3.00717
8	Public	Large	007	105	0.12515	7.99048
9	Public	Medium	302	89	0.22446	4.45506
10	Public	Medium	101	89	0.22446	4.45506
11	Public	Small	113	39	0.22478	4.44872
12	Public	Small	068	45	0.25937	3.85556

ANALYSIS

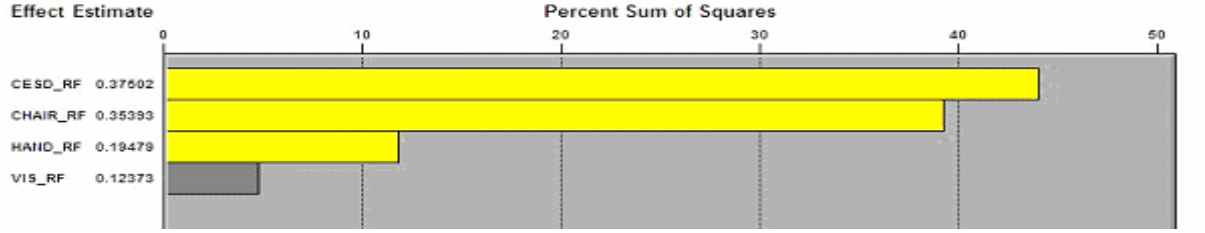
There are numerous methods available in the SAS/STAT® software to analyze clinical trial results, including the ADX interface when there is a continuous normally distributed outcome. For our Project Safety example, we illustrate the utility of the ADX interface main effect and Pareto plots. The main effect plots displayed in Figure 3 show the contribution of each risk factor to the number of falls. These plots help investigators quickly detect which risk factors may be strongly related to the number of falls.

Figure 3 Main effect plots for the relationship of selected risk factors with the number of falls in Project Safety.

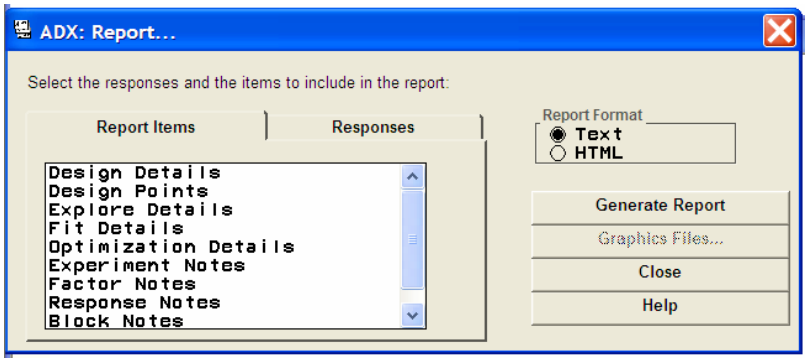


The Pareto plot (Figure 4) displays the estimates for removing each risk factor, as well as the contribution to the sums of squares for each studied risk factor. It is evident from the plot that the risk factor of depressive symptoms (CESD_RF) had the largest contribution to the sums of squares followed by weak lower body strength (CHAIR_RF) and then by weak upper body strength (HAND_RF). The gray bar represents the non-significant effect of poor vision on the number of falls.

Figure 4 Pareto plot of the contribution to the sums of squares for each risk factor related to falls in Project Safety.



The ADX interface also has a report feature that allows investigators to automate report writing by selecting the report items to include and saving the report as either a text or html format as displayed below.



CONCLUSIONS

The proper design of studies to evaluate multicomponent interventions in medicine permits the estimation of individual component effects. Because each component of an intervention adds to the cost and complexity in clinical trials, selecting the most effective components is critical. We have illustrated how several methods available in SAS can be used to more efficiently design these types of studies.

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