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COST EFFICIENCY UNDER NONPARAMETRIC SETUP FOR TWO-TREATMENT CLINICAL TRIALS

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Abstract

This article describes nonparametric procedure for comparing cost efficiencies among several repeated measurement designs under fixed total cost. Different models are assumed and related asymptotic results are provided. Method of allocating treatments is also obtained for two treatments with different costs per unit.

Introduction

Clinical study is an important area of research in modern days and the most important criteria is that it should be well supported by medical ethics. Sometimes the rule for allocating treatments under study may have greater role in controlling medical ethics specially when the study is based on repeated measurement design. It is well known that crossover design is better than parallel group design in this aspect. Again with the advancement of new scientific tools the scope of clinical research increases significantly. Thus, in clinical research, when two or more treatments are compared in a multi period design, the cost of conducting medical experiments also increase significantly. Therefore, it is required to develop statistical tools which provide a methodological suggestion in performing a certain clinical trial such that cost efficiency is achieved keeping in mind

the medical ethics of the trial. In this context, repeated measurement designs are considered to compare the cost efficiencies among them.

The organization of the rest of the chapter is as follows. Section 5.2 introduces different designs and the nonparametric models. Section 5.3 provides suitable cost function. Section 5.4 describes appropriate procedure for efficiency comparison. Simulation results are provided in Section 5.5. Allocation rule depending on costs of the two competitive treatments is provided in Section 5.6 for different crossover designs. The chapter ends with concluding remarks in Section 5.7, followed by some technical details in the appendices.

Designs and Models

In crossover trial, when two treatments A and B are compared, it may be better to re- strict ourselves up to three-period designs. This is because of the fact that in repeated measurement design dropouts of patients increase with the number of periods (Ebbutt, 1984). So two-period and three-period designs are considered such that the first two periods of the design constitute one of the basic crossover designs, viz., {AB, BA} (usual crossover design) or {AA, AB, BA, BB} (Balaam's design). See, for example, Balaam (1968), Chow and Lin (2000).

For two-period crossover design the possible choices are

- $D_{2.1}$ ={AB, BA}
- $D_{2.2}$ ={AA, AB, BA, BB},

whereas $D_{2.3}$ ={AA, BB} represents two-period parallel group design . In the literature of crossover design on three periods, the following designs

5.2. Designs and Models

- $D_{3.1}$ ={ABB, BAA}
- $D_{3.2}$ ={ABA, ABB, BAA, BAB}
- $D_{3.3}$ ={AAB, ABA, BAB, BBA}
- $D_{3.4}$ ={AAB, ABB, BAA, BBA}

e-ISSN 2320 –7876 www.ijfans.org
Research Paper
Vol.11, Iss.9, Dec 2022

are found as crossover designs and the design represented by $D_{3.5}$ ={AAA, BBB} is parallel group design.

Let Y_{jm} be the response of a patient corresponding to the j-th treatment sequence inperiod m. Define $Y^T = (Y_{j1}, Y_{j2})$ for two-period design (or $Y^T = (Y_{j1}, Y_{j2}, Y_{j3})$ for three-period design) and, as in the previous chapters, assume that

$$Y_j \sim G(x - \theta_{j1}, y - \theta_{j2}) \quad (5.2.1)$$

or

$$Y_j \sim G(x - \theta_{j1}, y - \theta_{j2}, z - \theta_{j3}) \quad (5.2.2)$$

according as the corresponding design is a two-period design or a three-period design, where G, the continuous bivariate (or trivariate) distribution function (d.f.), and $\theta_{jm} \in$ (treatment sequences), $m = 1, 2, 3$ are all unknown. Further, for $(-\infty, \infty)$, $j \in S$

some unknown univariate continuous d.f. F, the marginal d.f. of Y_{jm} is assumed to be

$F_m(x) = F(x - \theta_{jm})$, $j \in S$, $m = 1, 2$ (or $m = 1, 2, 3$).

In modeling θ_{jm}, apart from general effect μ and period effect π_m for the m-th period, some relevant treatment effects as direct treatment effect, self and mixed carryover effects are considered (see, for example, Candel, 2012; Kawaguchi et al., 2010; Liang and Carriere, 2010). As in Chapter 4, the corresponding comparisons between treatments B and A are denoted respectively by τ, λ and λ'. For illustration, under the additive assumption, θ_{jm}

in $D_{2.2}$ can be represented as follows:

Treatment Sequence (j)	*Period (m)*	
m = 1	m = 2	
AA (1)	$\mu + \pi_1$	$\mu + \pi_2$
AB (2)	$\mu + \pi_1$	$\mu + \pi_2 + \tau$

e-ISSN 2320 –7876 www.ijfans.org
Vol.11, Iss.9, Dec 2022

Research Paper

BA (3) $\mu + \pi_1 + \tau \quad \mu + \pi_2 + \lambda$

BB (4) $\mu + \pi_1 + \tau \; \mu + \pi_2 + \tau + \lambda'$

Notice that such model is not applicable in designs $D_{2.1}$, $D_{2.3}$ and $D_{3.5}$. Thus two model restrictions are considered as $\lambda' = \lambda$ and $\lambda' = \lambda = 0$. Denote the three models respectively by *Model 1*, *Model 2* and *Model 3*. The structure of θ_{jm} in other designs underdifferent models can similarly be defined.

Cost Function

Among the available works on cost efficiency in crossover design, Brown (1980) con- cent rates in $D_{2.1}$ under a simple cost structure consisting of equal cost for each period and for each treatment. Along this direction, Carriere and Huang (2000) provide com- parison of several crossover designs with respect to completely randomized design. Yuanand Zhou (2005) work on more general cost structure and compare several designs for fixed total cost. Candel (2012) suggests further generalization of the cost function and compares two-period designs. In this connection it would be important to mention that all such comparisons are done through variances of the direct treatment effects for which the assumption on the existence of second moment of the response variable is needed.

In this chapter, as in Yuan and Zhou (2005), the following cost function

$$C = Nc_0 + N \sum_{m=1}^{r} c_m \qquad (5.3.1)$$

is considered, where N denotes the total number of subjects involve in the trial; c_0 denotes the initial cost to recruit a subject in the trial; c_m denotes the cost of treating a subject inperiod m (= 1, · · · , r). It is assumed that $c_m = a + bm$, m = 1, · · · , r. Yuan and Zhou (2005) have also suggested to consider polynomial or exponential cost function wheneverrequired.

Comparison

The work compares cost efficiency of different designs under the chosen models fora given total cost. Here such comparisons are made by power study of suitably defined hypotheses

e-ISSN 2320 –7876 www.ijfans.org
Research Paper
Vol.11, Iss.9, Dec 2022

testing procedures. On this matter, assumption (5.2.1) or (5.2.2) is used to provide nonparametric tests for the global testing problem (see, for example, Tudor and Koch, 1994 among others) under different models mentioned below.

Model 1 : $H^1 : \tau = 0, \lambda = 0, \lambda' = 0$ Model 2 ; $H^2 : \tau = 0, \lambda = 0$
Model 3 : $H^3 : \tau = 0$

against composite alternatives H^l : not H^l, $l = 1, 2, 3$.

Now, based on different designs, between subject comparisons are used to develop asymptotically distribution free (ADF) tests for (H^l, H^l), $l = 1, 2, 3$ following the works given in Chapters 2 and 3. The procedures are illustrated in $D_{2.2}$ and are incorporated intoother designs. Here, instead of equal allocation (EA) scheme, equal probability allocation (EPA) scheme (as described by Bandyopadhyay et al., 2011 and provided in the earlier chapters) is adopted. In this scheme subjects (patients) under trial are distributed between two treatments completely at random. That means, if period 1 and period 2 assignment indicators are δ_1 and δ_2 with $\delta_s = 1$ or 0 according as a patient receives treatment A or B, $P(\delta_s = 1) = \frac{1}{2}$, $s = 1, 2$ and the response of a patient in period m is represented by

$$Z_{2,m} = \delta_1\delta_2 Y_{1m} + \delta_1 (1 - \delta_2) Y_{2m} + (1 - \delta_1) \delta_2 Y_{3m} + (1 - \delta_1) (1 - \delta_2) Y_{4m},$$

where Y_{jm} denotes the potential response to the treatment sequence j in period m, j = 1, 2, 3, 4 and m = 1, 2.

The present analyses are based on the data $(\delta_{is}, Z_{2,im})$, i = 1, 2 . . . N, s = 1, 2, m = 1, 2, obtained from N patients. Let n_A and n_B be the number of subjects to treatment A and treatment B respectively in period 1 and n_j be the number of subjects to the j-th treatment sequence in period 2, j = 1, 2, 3, 4. Then it is possible to write

$$n_A = \sum_{i=1}^{N} \delta_{i1} = N - n_B, \quad n_1 = \sum_{i=1}^{N} \delta_{i1}\delta_{i2} = n_A - n_2 \quad \text{and} \quad n_3 = \sum_{i=1}^{N} (1 - \delta_{i1}) \delta_{i2} = n_B -$$

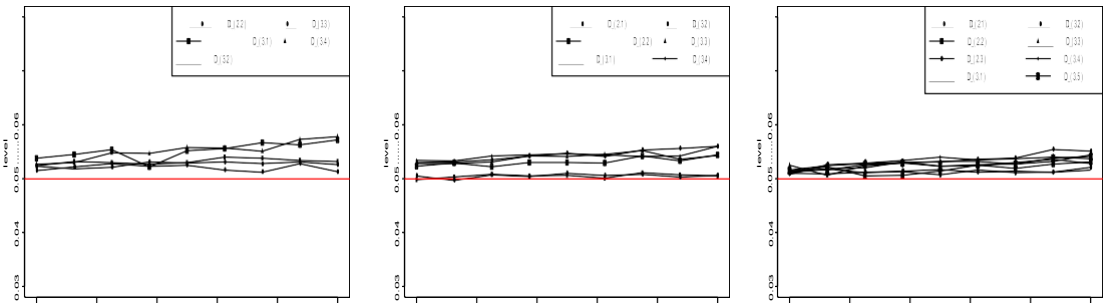
e-ISSN 2320 –7876 www.ijfans.org
Research Paper
Vol.11, Iss.9, Dec 2022

n_4.

Numerical Computation

the unknown quantities $\{c_{mm'}, m \neq m'\}$ are consistently estimated by $\{c_{mm'}, m \neq m'\}$

In a comparative study on cost efficiency among the designs, evaluation of competing type I error rate and power of various testing procedures is based on simulation. On this matter, for illustration, normal distribution (bivatiate or trivariate depending on the study periods) is assumed with an equicorrelated structure of the related variance matrix of the response variable and all the procedures are compared at the nominal level $\alpha = 0.05$. Here in which, for illustration, ^



0.0 0.2 0.4 0.6 0.8 1.0

b/a

(a) Under *Model 1*0.0 0.2 0.4 0.6 0.8 1.0

b/a

(b) Under *Model 2*0.0 0.2 0.4 0.6 0.8 1.0

b/a

(c) Under *Model 3*

Figure 5.1: Simulated type I error rates for $\rho = 0.5$, $C = 50000$, $c_0 = 500$, $a = 200$ with varying b

e-ISSN 2320 –7876 www.ijfans.org
Research Paper
Vol.11, Iss.9, Dec 2022

In this simulation study ten thousands iterations are made to generate data in the soft- ware **R** (version 3.1.2) with the help of the package *'mvtnorm'*. The total cost C and the cost parameters c_0, a and b are so chosen that the resulting sample size Nexceeds 20. Simulated type I error rates when the com- mon correlation coefficient (ρ) is 0.5, are displayed in Figure 5.1 under the three models for increasing per unit cost. It is observed that all the tests attain the nominal level satisfactorily, al- though there is a tendencyof overestimating the nomi-

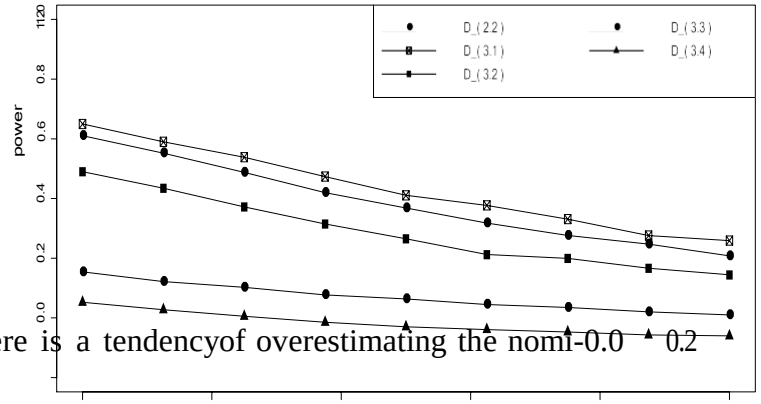


Figure 5.2: Comparison of the powers under *Model 1* for the alter- native $(\tau, \lambda, \lambda') = (1.0, 0.0, 0.0)$ for $C = 50000$, $c_0 = 500$, $a = 200$ with varying b

nal level for some of them particularly when the per unit cost is large (i.e. when N is small). Again, when N is small, inflated type I error rates are observed at $\rho \geq 0.8$ ($D_{3.2}$ and $D_{3.4}$ under *Model 1*) and at $\rho \leq 0$ ($D_{3.1}$, under *Model 2* and *Model 3*, $D_{3.3}$ under *Model 2* and $D_{3.4}$ under *Model 1* and *Model 2*). However, for moderately large sample size ($N \geq 26$) all the tests attain the nominal level satisfactorily at every choices of ρ (except tests for $D_{3.4}$ under *Model 1* which require slightly larger sample size, $N \geq 30$). In this connection it is important to mention that, for comparing the cost efficiency of the designs under EPA when sample size is small, it is suggested to use the estimated variance-covarianc

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Research Paper
Vol.11, Iss.9, Dec 2022

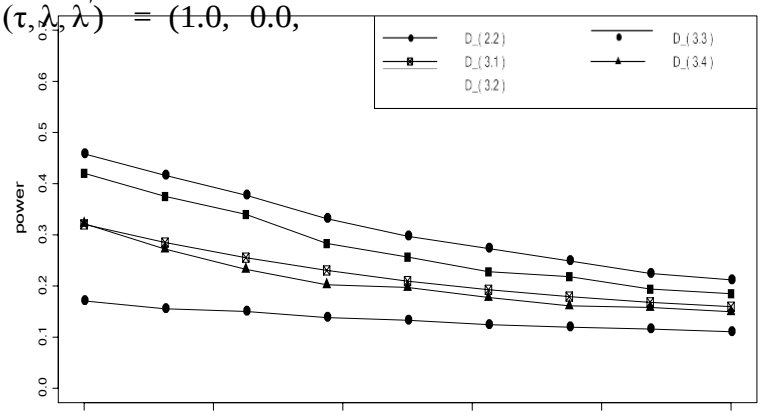
matrix of the MW-related statistics without making the assumption $\frac{n_j}{N}$

$\rightarrow 1\ (\text{or } 1), j \in S$

because this assumption makes the corresponding tests little conservative.

Note that efficiency of a design depends on the model assumption and it may vary withrespect to different treatment effects present in a model. Thus, to measure the effectivene of treatment parameters present in a model, the alternatives are taken in the following

way: $(\tau, \lambda, \lambda') = (1.0, 0.0,$



0.0 0.2 0.4 b/a

0.6 0.8 1.0

0.0), (0.0, 1.0, 0.0) and (0.0, 0.0,

1.0) for *Model 1*; $(\tau, \lambda) = (1.0,0.0)$ and (0.0, 1.0) for *Model 2*; $\tau = 1.0$ for *Model 3*. Now, in each model, power compari-son among the testing proce-dures from different designs

Figure 5.3: Comparison of the powers under *Model 1* for the alter-native $(\tau, \lambda, \lambda') = (0.0, 1.0, 0.0)$ for $C = 50000$, $c_0 = 500$, $a = 200$
with varying b
is made graphically for $\rho =$

0.5 and $C = 50000$. Depend-ing on the cost function, two
cost structures are chosen as *(i)* $c_0 = 500$, $a = 200$ and vary b as 0, 25, 50,…, 200; *(ii)* $a = 250$,

$b = 0$ and vary c_0 as 0, 100, 200,…, 1000.

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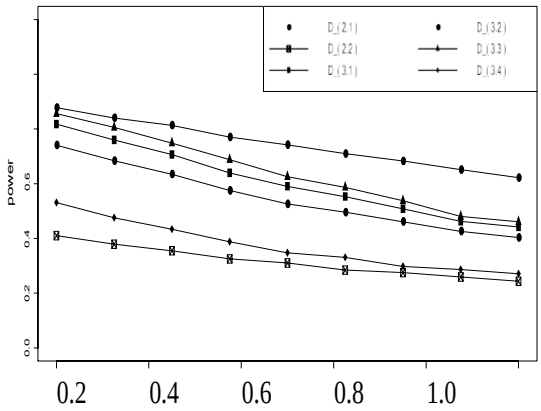
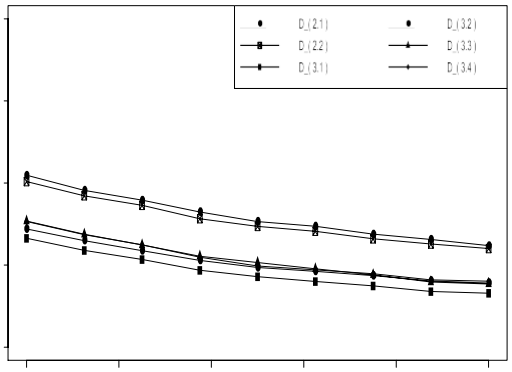
Research Paper
Vol.11, Iss.9, Dec 2022

It is observed that the con-figurations *(i)* and *(ii)* pro-vide exactly same conclusionregarding the cost efficiency. Hence, for illustration, the power plots corresponding to the first cost configuration are displayed. However, at the alternative (0.0,0.0,1.0), $D_{3.1}$ and $D_{3.4}$ have almost same cost efficiency and higher than the other designs (see Figure 5.4). Thus, to achieve cost efficiency under *Model 1*, one may have an open choice between $D_{3.1}$ and $D_{3.3}$ which perform relatively better than the other designs. It is also noticeable that Balaam's design ($D_{2.2}$) has the worst overall performance under *Model 1*.



(a) Under the alternative $(\tau, \lambda) = (1.0, 0.0)$



(b) Under the alternative $(\tau, \lambda) = (0.0, 1.0)$

Figure 5.5: Power Comparison under *Model 2* for C = 50000, c_0 = 500, a = 200 with varying b

Under *Model 2*, the performance of $D_{2.1}$ is better for both the alternatives (1.0, 0.0)and (0.0,

1.0). However, corresponding to $D_{2.1}$ and $D_{2.2}$, the two lines coincide to each other at the alternative point (0.0, 1.0) (see Figure 5.5b). But $D_{2.2}$ shows the worst per- formance at the alternative (1.0, 0.0). Thus to achieve higher cost efficiency in *Model 2*,$D_{2.1}$ is preferred. Under *Model 3*, $D_{2.1}$ shows superiority among the designs considered (see Figure 5.6). The performances of three-period designs are also satisfactory. However, parallel group designs have the worst performance under this model. In fact, it is observed that the performance of parallel group design decreases with the number of periods.

In this connection it is important to mention that, with conclusions remaining the same, the power of the tests increase with ρ (except for parallel group designs). Moreover, as mentioned ear-lier, the efficiency of a de-sign depends on the model assumption and it is difficult to make an overall conclu sion regarding the cost efficiency. However, it can be said that three-period crossover design performs better under the model containing complex carryover effects (*Model 1*). On the other hand, under simple model (i.e. *Model 2* or *Model 3*), the usual crossover design ($D_{2.1}$) is better.

For other designs, similar technique may be adopted to get the optimum proportion for allocating treatments. However, for $D_{2.1}$ under a given total cost C, it is possible to write $C = Nc_0 + N(c_A + c_B)$. Thus C is independent of any choice of p. Hence it is not possible to obtain an efficient allocation depending on the cost parameters and thus EPAdesign is the best possible option for allocating treatments.

However, for the three period crossover designs, it is possible to achieve cost efficient allocation in an analogous way as described for $D_{2.2}$. It is important to notice that, the treatment assignment indicators relate to the periods of randomization in which the costcan be controlled through allocation, whereas the costs of the other periods depend fullyon the previous period of randomization. Thus it is logical to take the periods where randomizations are made to provide test for (H^c_0, H^c_1). Applying the same technique to the three period designs the following solutions are obtained.

e-ISSN 2320 –7876 www.ijfans.org
Research Paper
Vol.11, Iss.9, Dec 2022

3 3.4 3.3

Notice that the range of p_{opt} for the designs $D_{3.i}$, i = 1, 2, 3, 4 is $\sqrt{(}\quad\sqrt{\quad})$ $2-\overline{1}, 2-\ 2\ .\overline{}$ This is because of the fact that for each of these designs there is a period where randomizationis not made and hence even when c_A and c_B are wide apart, consideration of the extremevalues of p_{opt} (i.e. close to zero or one) certainly do not lead to the efficient choice. The concept can also be extended in several directions.

Conclusion

In this chapter efficiency comparison among the designs with respect to cost is done un-der EPA when there is no difference between the cost in application of two competitive treatments. It is also shown that, when the costs in application of the two treatments aredifferent, EPA is not an efficient choice. However, as mentioned in Section 5.1, the most important criteria in clinical study is medical ethics. This is particularly important when a newly introduced drug is tested and we have no clear idea regarding the performance of it. Bandyopadhyay and Das (2017) provide a two stage allocation procedure to support medical ethics in this context but such allocation may not be cost efficient. However a more general allocation scheme would be that one which will provide a balance betweenthese two issues. Such things go beyond the scope of the present consideration and are kept for future research. Balaam's design ($D_{2.2}$) is supposed to provide more information with respect to carryover effects than $D_{2.1}$. From another viewpoint to achieve more precision from crossover study,it is advocated to apply crossover trial for more than two periods. Thus extension of thesimple crossover design ($D_{2.1}$) to three-period design will enable us to focus more lighton some complex carryover effects, e.g. higher order or long-term carryover effect along with simple carryover effect. However, such three-period design is not unique and the study requires a comparative approach through appropriate nonparametric procedures to investigate the superiority among these designs under different model assumptions. In the next chapter, we like to concentrate on such issues.

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