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Minimization in interventional trials: great value but residual vulnerability

Tom Treasure[a,*], Vern Farewell[b]

[a]Clinical Operational Research Unit, UCL (Department of Mathematics), 4 Taviton Street, London WC1H 0BT, UK
[b]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Cambridge CB2 0SR, UK

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In his commentary, Taves [1] has expressed the view that minimization should be the uniformly adopted way of assigning patients to treatments in comparative clinical trials, with a particular emphasis on the advantages of rank minimization. In advocating it as the ''platinum standard,'' Taves proposes that the question mark in the title of Treasure and MacRae's [2] editorial is to be removed.

Minimization has been usefully adopted in a variety of trials. It places overriding importance on the achievement of marginal balance with respect to patient characteristics in the treatment groups to be compared. One particular benefit of this is that of being able to demonstrate to skeptics that the treatment groups are otherwise comparable and that, therefore, any difference must be because of different assigned treatments. A second is that, in many circumstances, balance across important prognostic factors will provide an efficiency gain in the estimation of treatment effects and therefore provide a more powerful study.

Interestingly, there is a parallel with the arguments for randomization in experimental design. As outlined by Cox [3], there are two positive advantages to randomization. These are the following:

1. to ensure that the observed treatment effect provides a "good" (unbiased) estimate of the true treatment effect (i.e., the trial answers the right question),
2. to provide a means to measure the random error of the estimated treatment effect (i.e., to provide a basis for inference).

The second advantage facilitates certain types of statistical inference but is essentially a mathematical feature of randomization and so does not carry much weight on clinical or ethical grounds. From the medical perspective, the first advantage is of primary importance.

Taves argues that minimization also achieves the first advantage of randomization, which is essentially that of unbiased treatment allocation. The possibility of selection bias with minimization, by its nature, remains a possibility so the argument can never be ''open and shut.'' If there is any suspicion that the inclusion or exclusion of patients in the trial was amenable to manipulation in the light of knowledge of the likely next allocation, the fundamental principle, that there is no bias in the allocation, is jeopardized. There is no doubt that conscious or unconscious bias is a major problem in research, and it is naïve to think otherwise. Individual medical and nursing staff may exercise their biases for what they see as the highest of motives in caring for patients. That is perhaps why many experienced designers of trials prefer to introduce a degree of randomness into minimization by choosing the assignment that is most helpful to marginal balance with high probability but not with certainty. Perhaps this, along with the first benefit of minimization mentioned above, is sometimes cosmetic but a trial is successful only if it is broadly convincing so this is not unimportant. Thus, we would also advocate some degree of randomization when minimization is adopted.

A very useful reference for a discussion of how to deal with prognostic factors in clinical trials is Rosenberger and Sverdlov [4]. This article makes it clear that there are not always simple answers to how these should be incorporated into the design of trials. For example, they demonstrate that balancing on covariates may not always lead to the most efficient designs when nonlinear models are to be used. Careful technical investigations are required to address such matters, and there is a growing literature of this type related to minimization. Similarly, technical investigations of the loss in efficiency through the use of categorized continuous variables in analysis have been undertaken [5], but the extent to which these carry over to design has, to our knowledge, not been investigated. Thus the quantitative advantage of rank minimization compared with that based on categories is yet to be fully determined.

* Corresponding author. Tel.: +44 207 9283151; fax: +44 123 3740 378.

E-mail address: tom.treasure@gmail.com (T. Treasure).

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What is new?

Minimization is infrequently used. Discussion of this approach to unbiased allocation is to be welcomed, and we illustrate its application in the evaluation of interventions while adding some cautionary notes.

Rosenberger and Sverdlov [4] highlight that many views of minimization are expressed in ''opinion pieces'' and that ''the nonspecificity of language in these opinion pieces is becoming troubling.'' Taves' commentary [1] is quite appropriately an opinion piece and limited in its technical arguments but, nevertheless, we suggest that it is perhaps too early to assign ''platinum status'' to rank minimization on the basis of it and previous articles on the topic. Similarly, the advocacy of a two-stage analysis which gives separation between the primary trial analysis and the design in terms of the number of prognostic factors for which adjustment is made warrants further investigation before adoption, minimally with respect to some quantification of the inequalities associated with significance levels. In our ''opinion,'' we feel that balancing on an excessive number of factors is seldom necessary in practice.

We now consider the specific context of surgical trials. It is 15 years since *The Lancet* published an inflammatory editorial likening surgical research to ''Comic Opera'' [6]. The grounds for criticism were Horton's finding a plethora of case series and a dearth of controlled trials in recent surgical journals. It is true that much of surgical practice is based not on evidence from clinical trials but on the repeated fixing of a problem in a rather obviously mechanistic and reproducible way. Where the cause and effect relationship between surgical endeavor and clinical outcome is less clear, a controlled trial is needed. Any means that leads to randomized controlled trials in surgery being more often done, and that might help to give clinically useful answers with relatively small numbers, is welcome. The truism ''some unbiased evidence is clearly better than none'' [7] makes it worth striving to ensure that allocation bias is seen to be excluded. Thus, the advantage of minimization in ensuring balance is very attractive.

This is particularly true in cancer surgery where it has become impossible to discern ''signal from noise'' [8] for a whole list of reasons. There is wide variation in cancer stage at presentation and in its rate of progression. The better cases are selected by experienced and highly intelligent clinicians for their more demanding treatments, and they may well know how to pick winners. It is then impossible to separate selection for the treatment from the effect of the treatment: the fact that surgery was performed may be associated with a better outcome than seen in patients not selected, rather than that the act of surgery gave the benefit. The degree of selection cannot be estimated and may be only a few percent of possible candidates. In follow-up studies, the size of the denominator is rarely stated and is often unknown or unknowable. It also is in the nature of follow-up studies that the patients to be included are identified by having completed treatment rather than on intention to treat. There is a current mind-set of throwing everything at the cancer: multiple therapies are used in sequence or in combination. The completion of treatment takes time and involves sequential selection, thus further associating treatment with survival while not necessarily influencing it. Contemporary notions of ''personalised'' therapy further confuse the picture: treating by protocol is deliberately set aside as the clinician applies successive treatments by ''clinical judgement.'' There are thus many ways in which there is an illusion of benefit greater than the reality [9]. Taking asbestos-related cancer as an example, it is generally accepted by surgeons and pathologists that, at a mechanistic level, even the most radical surgery consistently fails to clear pleural mesothelioma and so fails in the primary objective of all cancer surgery [10]. Yet a survey of 802 thoracic surgeons revealed that 50% of American surgeons believed that mesothelioma could be cured by surgery alone [11,12].

It was against such a background that the Mesothelioma and Radical Surgery (MARS) trial was performed. MARS, the only surgical study of mesothelioma ever to include a randomized control group, found that those who had the chemotherapy without the surgery fared better in terms of both survival and quality of life, but only if adjustment was made for gender, histological subtype, stage, and age at randomization. Unadjusted survival was not significantly different ($P = 0.08$) [13]. MARS was of necessity a small trial with 50 patients and might have been seen as a prime candidate for minimization. Although it must be remembered that, in some cases, adjusted and unadjusted analyses simply answer different questions, in this case, the difference between these two analyses might yet undermine the impact of the trial. We cannot know what would have happened if minimization had been used but preventing a problem is usually better than fixing it later.

Minimization offers the opportunity to ensure balance between the groups. Unlike laboratory scientists who can study rats of the same sex, age, and of similar weights, clinical researchers' subjects come in all shapes and sizes, with a range of patient-related factors that may have a larger effect on the outcome of interest than the likely difference between the two interventions. For example, in the choice between heart valves the variations in outcome attributable to the patients' age and left ventricular function were likely to be greater than the differences attributable to the subtleties of valve design [14]. Based on follow-up studies from different eras, and with differing case mix, there was a perception that one valve performed better than another. When these patient-related factors were balanced by minimization, and a controlled trial was performed, the believed difference in outcome between the valves disappeared and tended to reverse [15].

In our own present surgical study of pulmonary metastasectomy in colorectal cancer (PulMiCC) [16,17], we know

that there are several factors which have been established repeatedly in multivariable analysis to influence outcome, including the number of metastases, the time course of their appearance, the level of carcinoma embryonic antigen, and the patient's age and sex, and we will include them in the allocation by minimization, which combines an element of randomization. It is a multicenter study, and the computation is made at the trial center, and no participants have access to the data or details of computation.

The need for controlled studies now is even greater than back in the day of writing "Comic Opera," but the 50% chance by random allocation to *not* receive an intervention is perceived by many clinicians as an insurmountable obstacle to recruiting patients into studies. It is usually said that patients will not accept "random" allocation of treatment, but this was not the experience in MARS [13]. We believe more of a problem is clinicians' or surgeons' reluctance to accept uncertainty and to make an explicit declaration to the patient that there is doubt. In PulMiCC, we recognize that recruitment of patients is likely to be slow and arduous, and eventual numbers are likely to be modest. Any imbalance in the groups will allow those who do not like the result to explain it away, and all our efforts will be wasted. A group of patients allocated in an unbiased way into two groups willing to be cared for within a trial protocol is a scarce and precious resource.

Minimization is a creative contribution to the design of clinical trials and can offer some significant potential advantages. At the same time, there are many factors that can influence the design of trials, and no design can anticipate all the "surprises" that the conduct of a trial may reveal. Given this, and the lack of definitive technical information concerning its use, it is pragmatic to make use of minimization when it will be particularly helpful but to refrain, for now, from assigning it platinum status.

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