Recruitment in Clinical Trials: The Use of Zelen’s Prerandomization in Recent Neurovascular Studies

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OBJECTIVE: Randomized allocation of treatment options is not well accepted within the clinical community. Some methods of implementation may be received more favorably than others. Prerandomization may be an acceptable means to facilitate recruitment in some clinical trials.

METHODS: We first compare randomization and prerandomization using illustrative neurovascular trials. We review some problems with conventional trials, Zelen’s prerandomization as an alternative method, and the ethical issues that have surrounded prerandomization since its inception in a historic trial. Conventional and Zelen’s randomization are then compared with other means to provide and verify care in the context of clinical uncertainty.

RESULTS: The major problem with conventional randomization is that consent is requested for 2 management options, one of which the patient will not receive. The problem with prerandomization is that treatment is allocated before the patient has consented to trial participation. Prerandomization may trade recruitment difficulties for excessive crossovers. However, other ways to practice under uncertainty and verify patient outcomes, such as case series and registries, are more ethically and scientifically problematic.

CONCLUSIONS: Until the ethical functions of randomized allocation of selected treatment options in the care of patients are recognized by the neurovascular community, Zelen’s prerandomization may help recruitment into difficult trials and contribute a means to provide best possible care in the presence of uncertainty.

INTRODUCTION

Randomized control trials (RCTs) are often conceived as tools that can provide reliable knowledge to inform how we should care for future patients. Thus trials are designed such that their results should impact clinical practice in the future. What is less well recognized is that when the proper way to act is unknown or controversial, the uncertainty is reason enough for medical practices to be altered immediately: the patient should be included in a trial, now conceived as the prudent way to guide such practice under uncertainty, to provide best care for the patient long before the trial results become available.¹

Randomization remains unpopular in the neurovascular community, especially when trials question the merit of interventions that have already been, rightly or wrongly, integrated into care, such as the preventive coiling of unruptured aneurysms² or endovascular treatment of brain arteriovenous malformations.³ The consequence is that few such trials are designed, few patients are recruited, and most patients continue to receive interventions that have never been proven beneficial.⁴ This is unvalidated care.

Prerandomization was conceived by the late Professor Marvin Zelen to overcome problems with recruitment in RCTs. It involves seeking consent after randomized allocation of a treatment option.⁵ Prerandomization has not commonly been used in neurovascular trials; the Barrow Ruptured Aneurysm Trial...
Better outcomes with coiling. For many surgeons, an important concern was that a large number of patients treated at trial centers had not been included in the trial. Eligibility for ISAT required that either treatment would be a suitable option for each patient, and most patients expect that surgeon to follow the verdict of his judgment and personal preferences. As we have seen with BRAT, this problem is minimized when the doctor can claim to make, “as in daily practice, a treatment decision based on what he believed would provide the best outcome for that particular patient.” The burden of uncertainty placed on the patient is lessened.

Two other problematic issues with conventional RCTs arise when studies assess multiple, widely different treatment choices (such as TOBAS, which includes observation, surgery, embolization, radiation therapy, and their combinations), which are not necessarily available or applicable for each patient. The first is an
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