



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

Key words

- Consent
- Randomized controlled trial
- Research ethics
- Vascular diseases

Abbreviations and Acronyms

BRAT: Barrow Ruptured Aneurysm Trial
ISAT: International Subarachnoid Aneurysm Trial
NSABP: National Surgical Adjuvant Breast and Bowel Project
RCT: Randomized control trial
SACPD: Single arm consent prerandomized design
TOBAS: Treatment of Brain AVMs Study

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(BRAT) study is one example that will be discussed.⁶ As a result of the recruitment difficulties encountered by previous investigators, the Treatment of Brain AVMs Study (TOBAS) was designed to include prerandomization.^{3,7} Even more recently, prerandomization has been proposed to encourage clinicians to offer flow diversion only as a randomized alternative to more conventional treatment options,⁸ or to ease the conduct of difficult aneurysm trials.^{9,10}

The contrast between conventional and prerandomized (or Zelen's) trials are not well understood; the increasing usage of prerandomization in neurovascular trials may call for a reappraisal of their potential advantages and disadvantages. In this article we review problems with conventional and Zelen's trials. Prerandomization has been controversial since it was first used in the historic National Surgical Adjuvant Breast and Bowel Project (NSABP) study.¹¹ We will defend prerandomization because, compared with other ways to practice unvalidated interventions, it may help deliver verifiable care in the context of serious uncertainty, and in the best medical interest of current patients.

BRAT AND THE INTERNATIONAL SUBARACHNOID ANEURYSM TRIAL (ISAT)

We start by contrasting randomization and prerandomization as used in 2 trials on ruptured aneurysms.^{6,12} Until the early 1990s, aneurysms were treated by surgical clipping. Endovascular coiling, a less invasive approach, was rapidly adopted in many centers, but it remained unknown which approach led to better clinical outcomes. ISAT, the conventional RCT published in 2002, showed better outcomes with coiling.¹² For many surgeons, an important problem remained: should all patients now be offered coiling? The 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 each patient had to consent to both clipping and coiling. More than 9559 aneurysms were screened, but only 2143 (22.4%) patients were enrolled, affecting the generalizability of trial results.

BRAT addressed this problem by studying all patients with aneurysmal subarachnoid hemorrhage, then using Zelen's prerandomization, although not by name "...patients were assigned to a surgeon with a prestated treatment intent (coil or clip), but before embarking on that intended treatment, the assigned surgeon would naturally, as in daily practice, make a treatment decision based on what that practitioner believed would provide the best outcome for that particular patient. This decision may be to proceed with the intended or assigned treatment, or it may be that surgeon's judgment that a particular patient would be better served by the other treatment modality, in which case the patient would 'crossover' to the alternative treatment."⁶

In BRAT, some patients happened to arrive on surgical days. They were told that surgery would, in the surgeon's mind, "provide the best outcome for that particular patient." This was true of 98% of patients allocated to surgery. Other patients arrived on endovascular days; they were further selected to be the cases best treated with coiling, and those selected patients (62%) were told that coiling was believed to provide the best outcome for their

particular case. Other patients (38%) were instructed to crossover because the surgeon believed this was best.

What is the difference between ISAT and BRAT? Both used randomized allocation of treatments, and both led to similar conclusions. But if few ISAT patients were recruited (22%), once enrolled, almost all received the treatment they were allocated (98%).¹² In contrast, 500 of 725 screened patients (69%) consented to BRAT. Surgeons, however, chose to instruct patient to crossover in 40% of patients allocated to coiling. As far as we can tell from the report, only 1 patient refused the treatment assigned by the surgeon. It is apparent that the beliefs and preferences of clinicians and patients led many to opt out of the ISAT trial. The care provided to patients outside of ISAT remains unvalidated and unverifiable care. Patients and clinicians certainly seemed more comfortable to participate in BRAT. Unfortunately, as we will see, prerandomization may trade a problem of recruitment for a problem of crossovers.¹³

THE PROBLEMS WITH CONVENTIONAL RCTs

Reasons for poor recruitment in a conventional RCT were investigated at the time of the NSABP study,¹¹ a trial on breast cancer surgery that was saved by prerandomization.¹⁴ The predominant reason for doctors not to include eligible patients in conventional RCTs was the necessity to divulge to patients the uncertainty regarding the best management. At the time, this was considered barely compatible with a conventional doctor-to-patient relationship.¹⁴

Uncertainty in medicine is everywhere: in explaining risks of surgical procedures, in discussing outcomes or prognosis. The main difference between those apparently acceptable uncertainties and the one involved in trial participation is that, in the conventional doctor-to-patient relationship, by opting for 1 treatment, the doctors seem to overcome the uncertainty. In conventional RCTs, the uncertainty seems to win: the doctor will follow the verdict of the randomization scheme. This is a dramatic change for physicians accustomed to authority in choosing a course of action. Most clinicians are trained to believe a single best treatment choice can be found and acted on for each patient, and most patients expect this ability from their physician. A recent report on patients' perspectives regarding a "learning health system" found that patients were concerned that randomization may undermine "individualized care that acknowledges their unique medical histories."¹⁵

Randomized allocation of treatment options is thus considered "foreign" or unnatural in the context of care,¹⁶ because it seems incompatible with individualized choices based on clinical 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 all necessarily available or applicable for each patient.⁷ The first is an

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