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Re-randomization increased recruitment and provided similar treatment estimates as parallel designs in trials of febrile neutropenia

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Abstract

Objective: Re-randomization trials allow patients to be re-enrolled for multiple treatment episodes. However, it remains uncertain to what extent re-randomization improves recruitment compared to parallel group designs or whether treatment estimates might be affected.

Study Design and Setting: We evaluated trials included in a recent Cochrane review of granulocyte colony-stimulating factors for patients with febrile neutropenia. We assessed the recruitment benefits of re-randomization trials; compared treatment effect estimates between re-randomization and parallel group designs; and assessed whether re-randomization led to higher rates of non-compliance and loss to follow-up in subsequent episodes.

Results: We included 14 trials (5 re-randomization and 9 parallel group). The re-randomization trials recruited a median of 25% (range 16−66%) more episodes on average than they would have under a parallel-group design. Treatment effect estimates were similar between re-randomization and parallel group trials across all outcomes, though confidence intervals were wide. The re-randomization trials in this review reported no loss to follow-up and low rates of non-compliance (median 1.7%, range 0−8.9%).

Conclusions: In the setting of febrile neutropenia, re-randomization increased recruitment while providing similar estimates of treatment effect to parallel group trials, with minimal loss to follow-up or non-compliance. It appears to be safe and efficient alternative to parallel group designs in this setting.

Keywords: Re-randomization; Randomized controlled trials; Clinical trials; Febrile neutropenia; Re-enrolment; Poor recruitment

1. Background

Febrile neutropenia occurs when neutropenic patients (those with abnormally low neutrophil granulocyte counts) develop fever. It is often a complication for patients with cancer who receive chemotherapy regimens which suppress bone marrow activity. Because chemotherapy is usually given in multiple cycles, patients may develop febrile neutropenia multiple times during the course of their cancer treatment, and each episode of febrile neutropenia would require medical intervention. Standard care for febrile neutropenia is broad-spectrum antibiotics [1]. However, it has been suggested that granulocyte colony-stimulating factor (G-CSF) could be useful in this setting, as it regulates the production of the neutrophil lineage [1]. A number of clinical trials have compared the use G-CSF with antibiotics vs. antibiotics alone in patients with febrile neutropenia.

In a parallel group trial, patients would be enrolled for one episode of febrile neutropenia only; if they experienced further episodes of febrile neutropenia, they would no longer be eligible to participate in the trial. This approach can be inefficient, as a large proportion of febrile

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What is new?

- Previous work has shown that re-randomization trials can provide unbiased estimates of treatment effect and increase patient recruitment, but this has never been evaluated empirically.
- Our review found that re-randomization trials increased patient recruitment while providing similar estimates of treatment effect to parallel group designs, with minimal loss to follow-up or non-compliance.
- Re-randomization appears to offer a safe and efficient alternative to parallel group trials.

neutropenia episodes may be ineligible for the trial, which can affect recruitment. The majority of trials in this area have recruited fewer than 50 patients per treatment arm [1], which would lead to underpowered analyses for important outcomes such as mortality.

An alternative approach is a re-randomization trial (Fig. 1) [2–4]. In re-randomization trials, patients can be re-enrolled and re-randomized for each new episode of febrile neutropenia they experience. The number of times each patient is enrolled in the trial is not specified in advance, but instead depends on the number of febrile neutropenia episodes they experience during the course of the trial; some patients may be enrolled only once, and others may be enrolled multiple times. Because patients can be enrolled for multiple episodes, re-randomization can increase the recruitment rate compared to parallel group designs, which could facilitate quicker and more efficient trials [2,3].

However, there has been little empirical evaluation of re-randomization trials, and so, it is unclear how much of a recruitment benefit might be expected in practice or whether treatment effect estimates from re-randomization trials might differ to those from parallel group designs.

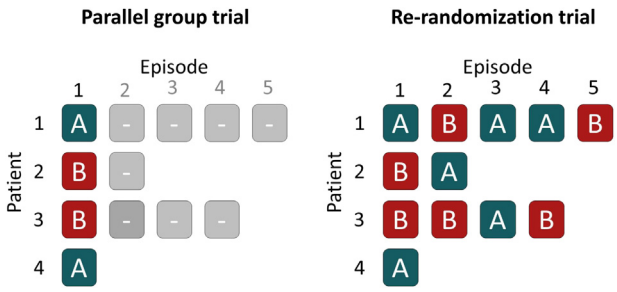

Fig. 1. Re-randomization vs. parallel group trials. This figure depicts the treatment episodes occurring during the trial recruitment period that are eligible for enrollment under a parallel group and re-randomization design. Gray episodes denote the patient was not eligible, A = allocated to treatment A, B = allocated to treatment B.

Furthermore, there may be concern that repeated enrollments in re-randomization trials may place undue burden on patients due to increased treatment or follow-up burden and may lead to higher rates of non-compliance or loss to follow-up in subsequent enrollments. We there undertook a review of trials in febrile neutropenia to evaluate (1) the impact re-randomization had on recruitment; (2) whether treatment effect estimates from re-randomization trials were different to those from parallel group trials; and (3) whether re-randomization led to higher rates of non-compliance and loss to follow-up in subsequent episodes.

2. Methods

2.1. Overview of re-randomization trials

We begin by providing a brief overview of the re-randomization design (Table 1). This design is appropriate in settings where at least some patients may require treatment on multiple occasions, and in practice, the intervention(s) under study would be used for each new treatment episode that occurred [2,3]. Furthermore, the duration of the intervention and the length of the patient follow-up period must be less than the overall length of the trial recruitment period [2,3]. This design is therefore suitable in the setting of febrile neutropenia, as some patients experience multiple episodes and require treatment for each episode, and the intervention (G-CSF) and patient follow-up duration are typically short-term.

There are two core design requirements for re-randomization trials [2,3]; (1) patients are only re-enrolled and re-randomized after the follow-up period from their previous enrollment is complete (i.e., there cannot be overlapping follow-up periods from different enrollments); and (2) randomizations for the same patient are performed independently (e.g., patients are not forced to crossover from one treatment arm to another between episodes).

Analysis of re-randomization trials can be via an "independence" analysis [2], where each episode is analyzed independently (i.e., the correlation between episodes from the same patient is ignored in the analysis). This approach can provide unbiased estimates and correct type I error rates [2]. It will also provide the same power as a parallel group design with an equivalent number of observations in many settings, provided the overall variance is not increased through the use of re-randomization; further details are available in another article [2]. Therefore, in these settings, the same sample size calculation as in a parallel group design could be used; however, instead of recruiting the required number of patients, the re-randomization trial could recruit the required number of treatment episodes. For example, if the sample size calculation for a parallel group trial required 100 patients, a re-randomization trial would require 100 episodes of febrile neutropenia from fewer patients, for example, 100 episodes from 75 patients (where 50 patients