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RESEARCH ARTICLE

Interim sample size reestimation for adequately powered series of N-of-1 trials

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KEYWORDS:
N-of-1 trials; Sample size reestimation; Simulation study;

1 | INTRODUCTION

Randomized controlled trials (RCTs) are considered the gold standard in determining treatment efficacy in healthcare. At first glance, these standard RCTs seem to earn their position, as the randomization of patients into a parallel experimental and control condition works quite well in controlling factors that are not under experimental control, creating the possibility to make causal inferences about the usefulness of the intervention. A drawback, however, is that these standard RCTs require a relatively large sample size to establish the effectiveness of treatment with sufficient power. In all instances it is desirable to limit the number of subjects to enter a medical study, as it exposes individuals to potentially inferior treatment. However, for the instances of finding the right intervention for patients with rare diseases, standard RCTs become unfeasible due to the relatively large sample size it requires. As populations of patients with rare diseases only have a limited number of people that could enter such a experimental study, alternatives should be sought to obtain reliable estimates of the treatment effect.

A clinical trial methodology that offers the possibility to reduce the number of subjects necessary to find a treatment effect with sufficient power, is the N-of-1 trial. The N-of-1 trial is a randomized controlled multiple crossover trial where a single patient repeatedly receives the experiment and control intervention in a random order, spread out over multiple cycles[1]. As

the experiment is conducted within a single patient, the advantage of the N-of-1 trial is that a patient-specific treatment effect estimate is obtained. Often, clinical evidence that is generated by standard RCTs turns out to have poor generalization and is therefore to a limited amount applicable to patients in ordinary practices[2]. Also, treatments that are shown to be safe on average, may have a disbalance in risks and benefits to individual patients[3]. With an N-of-1 trial, these issues can be avoided by purely estimating the effect of treatment on a single patient.

To obtain reliable results, N-of-1 trials should be performed under specific clinical circumstances. First of all, the disease under study should be long term, symptomatic and stable over time in order to avoid that the treatment differences will be obscured within and between cycles due to disease progression. Second, the intervention should not modify the course of the disease and should have a rapid on- and offset of biological action of the medication[4,5].

A single N-of-1 trial does not compare itself with a standard RCT, as the results of a single trial are specific to an individual patient, and hence, cannot be generalized to the population. However, when the results of several separate N-of-1 trials are combined it is possible to estimate the population treatment effect[6]. Even though every patient is unique, there is also some similarity in the disease progression and the treatment response of patients. In the combined analysis of separate N-of-1 trials, both the magnitude of the treatment effect as well as the heterogeneity in treatment response are taken into account[6]. The combined estimate of the separate trials forms the basis of knowledge about the treatment, whereas the estimate of the heterogeneity in treatment response allows for determining optimal treatment for every single patient by balancing the similarities and differences.

Combined N-of-1 trials, now referred to as series of N-of-1 trials, have been performed in, inter alia, studying the influence of Mexiletine on nondystrophic myotonia[7], studying the effectiveness of Methylphenidate on fatigue in patients with end-stage cancer[8], an for investigating the usefulness of Sildenafil on Raynaus-Phenomenon patients[9].

require a smaller sample size compared to standard RCTs, as every patient serves as its own control.

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