

## 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; statistical methods;

## 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 balancing factors that are not under experimental control, allowing for unbiased estimation of the population treatment effect. A drawback, however, is that these standard RCTs require a relatively large sample size to establish the effectiveness of treatment with sufficient power. For the instances of finding the right intervention for patients with rare diseases, i.e., small patient populations, standard RCTs become therefore unfeasible.

A clinical trial design 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 experimental and control intervention in a random order<sup>1</sup>. 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 the general population<sup>2,3</sup>. This imposes challenges to the usefulness of standard RCT findings in evidence-based medicine. One-size-fits-all does not always apply in practice.

There are some essential clinical conditions that are suitable for the use of a N-of-1 trial. First, the medical condition for which the intervention is prescribed should be chronic and (relatively) stable over time in order to reduce the chance that the progression of the disease can obscure the treatment differences between and within the trial cycles<sup>4,5</sup>. Moreover, the intervention being tested in the N-of-1 trial should have a rapid on- and offset of biological action, and should have a short half-life to ensure that there is rapid washout as the cycles alternate<sup>5</sup>. Additionally, the effect of the intervention should be measured using a validated (clinical) outcome measure (e.g., choosing the right scale ensuring that real benefits and real burdens are being measured). Lastly, the intervention used in the study should not alter the underlying condition, as this will make it unable to interpret the results for an individual as the trial progresses<sup>5</sup>. This all necessitates careful selection of participants, short time cycles and relatively stable symptoms.

As results of a single N-of-1 trial are specific to an individual patient and can therefore not be generalized to the population, a N-of-1 trial does not compare itself with a standard RCT. However, combining several separate N-of-1 trials, under the condition that the trials are identical, creates the possibility to estimate the population-level treatment effect<sup>6</sup>. In the combined analysis of separate N-of-1 trials, now referred to a series of N-of-1 trials, both the magnitude of the average treatment effect as well as the heterogeneity in treatment response are taken into account<sup>6</sup>. Comparing multiple treatment cycles combined with the recognition that the variability in response within individuals is typically lower than the variability between individuals, a smaller sample size is required to detect an effect of treatment in series of N-of-1 trials compared to parallel RCTs<sup>5</sup>. This makes series of N-of-1 trials a valuable alternative to standard RCTs in the accumulation of a comprehensive evidence base in populations of people with rare diseases.

These series of N-of-1 trials have been performed in, among others, studying the effect of mexiletine on nondystrophic myotonia<sup>7</sup>, studying the effectiveness of methylphenidate on fatigue in patients with end-stage cancer<sup>8</sup>, and for investigating the usefulness of sildenafil on Raynaud-Phenomenon patients<sup>9</sup>. Reasons for choosing the N-of-1 trial methodology vary, in general but also specifically for these aforementioned studies. The latter study chose to conduct a series of N-of-1 trials due to the heterogeneity in treatment response that should be taken into account, whereas the first two studies chose for the N-of-1 trial methodology due to inability to achieve the required sample size for a standard RCT.

As in any clinical study, a priori sample size determination is necessary to avoid under- or overpowering the study, for planning on allocating resources and for assessing the feasibility of the study. Sample size formulas have been derived for series of N-of-1 trials for both random and fixed effects models<sup>10</sup>. As the main objective of combining the results of separate N-of-1 trials is to make inferences regarding the population treatment effect, random effects models are most appropriate and of interest here. For the sample size calculations, assumptions have to be made with regard to the parameters in the model, such as the clinically relevant difference and the nuisance parameters. However, the nuisance parameters in the model, which concern the within- and between subject variance of the response to treatment for series of N-of-1 trials<sup>11</sup>, are generally unknown at the start of the study. Taking estimates of nuisance parameters from other studies can be unreliable because of differences in the study population, background conditions or study design<sup>12</sup>. Furthermore, an estimate of the between subject variance in treatment response is often not available because the kind of study to obtain these estimates is a trial (or trials) incorporating such a component, such as a series of N-of-1 trials<sup>13</sup>. Series of N-of-1 trials are not (yet) that common, and even if similar series of N-of-1 trials exist, these kinds of estimates are usually not reported in the literature. Making unrealistic assumptions for these nuisance parameters can lead to substantial over- or underpowering, where the former exposes too many patients to potentially inferior treatment and the latter increases the risk of failing to identify a clinically relevant treatment effect due to a lack of power.

An appealing strategy for conquering the problem of incorrect assumptions for unknown parameters in sample size calculations is a two-stage design with interim sample size reestimation based on nuisance parameter estimates. With this design, the initially required sample size is calculated by making reasonable assumptions for the unknown nuisance parameters. Then, a portion of the data is collected up until a prespecified interim point along the trial and the unknown nuisance parameters are estimated. These estimates are then used to update the power analysis and to adjust the sample size. Subsequently, the study is continued until all required participants are observed, and finally, the hypothesis is tested with all the data<sup>14</sup>. Simulations studies have shown that this method has a high potential to protect from an incorrect sample size if the nuisance parameters were misspecified at the design stage of the study<sup>15</sup>. A distinction can be made between interim sample size reestimation based on nuisance parameter estimates and based on treatment effect estimates<sup>16</sup>. This thesis will not cover the latter approach.

A concern with interim sample size reestimation based on estimates of nuisance parameters, is the inflation of the type I error rate<sup>17,15,18</sup>. Investigating the influence of interim sample size reestimation for series of N-of-1 trials on the type I error rate is

not the main objective of this thesis. However, it will be assessed whether the type I error rate becomes inflated for specific scenarios considered here, allowing future research to build upon these results.

The application of interim sample size reestimation has not yet been investigated in the context of series of N-of-1 trials and no specific guidelines have been established. With the use of simulation studies, guidelines for the minimally required sample size for sample size reestimation in series of N-of-1 trials will be established, and series of N-of-1 trials incorporating interim sample size reestimation will be compared with series of N-of-1 trials having a fixed sample size. Power and expected sample size are important measures of performance herein. Furthermore, the type I error rate for series of N-of-1 trials incorporating interim sample size reestimation will be evaluated.

The remainder of this thesis will be structured as follows: In section 2, notation, sample size calculations for series of N-of-1 trials, and the model that is used for the simulation studies are discussed. In section 3 the design of the simulation studies in which power, expected sample size and the type I error rate are evaluated will be explained. Section 4 discusses the results of the simulations studies. And finally, this thesis is concluded with a discussion which is outlined in section 5.

## 2 | METHODOLOGY

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## 3 | SIMULATIONS

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## 4 | RESULTS

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## 5 | DISCUSSION

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