Thesis Proposal

Naomi Smorenburg | 5506719
Methodology & Statistics for the Behavioral, Biomedical & Social Sciences
Supervisors: Rutger van den Bor & René Eijkemans

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Using a Decision-Theoretic Approach to Optimize Design Characteristics in Rare Disease Trials

A clinical trial is an experimental study, in which new treatments or interventions are tested. Clinical trials are needed to generate data on the safety and efficacy of new medical treatments, and their design characteristics (e.g. sample size requirements and follow-up duration) are typically determined on the basis of statistical error rates.

Under some circumstances these standard methods might be inadequate, for example in a rare disease setting, where the required sample size obtained can be unrealistically high.
A rare disease was defined by the *Orphan Drug Act* of 1983 as a disorder or condition that affects less than 200,000 persons in the United States [2]. In the European Union, a disease is defined as rare if the prevalence is not more than 5 in 10,000 [9]. The amount of rare diseases worldwide is estimated to be around 7000, so in total a substantial amount of people will be affected by a rare disease at some point in their lives [9]. Both the Food & Drug Administration (FDA) and European Medicines Agency (EMA) stated that less commonly seen methodological designs may be acceptable in small population conditions if they might improve the interpretability of the results in the study [1].

Alternative approaches
As stated above, the classical approach for determining sample size in clinical trials is based upon statistical error rates. Alternative approaches for sample size calculations in rare disease settings have been proposed, for example the *decision theoretic approach* [3]. *Decision theory* is a statistical technique by which the problem of decision-making under uncertainty may be formalized. The consequences of different design options are expressed in terms of a *utility* function, which depends on the true (but unobserved) treatment effect. Comparing expected utility values for different actions (like choice of sample size, and follow-up), enables the optimal action to be determined [4].

ALS
An example of a rare disease is Amyotrophic Lateral Sclerosis (ALS). ALS is one of the most severe and invalidating diseases of the nervous system [5]. Each year, 300 to 400 people are diagnosed with ALS in the Netherlands and approximately 6,000 people are diagnosed in the U.S.A [8]. The average survival time is only three years. Up until now, no effective treatments exist [6].

Research setting

In this research, the following setting will be assumed. Suppose a randomized clinical trial is conducted in a rare disease setting such as ALS, with the aim of demonstrating superiority of experimental treatment ***E*** over the standard of care ***C*** (see figure 1) in terms of survival. All patients with disease onset between two specific timepoints (t_0 and t_1), will participate in the trial and are randomly assigned to either ***E*** or ***C***. These patients are then followed till the end of the trial (t_2). Patients with disease onset between t_1 and t_2 will continue to receive ***C***. After the trial, all patients, depending on the outcome of the trial (***E*** is proven to be superior, or not), will receive ***C*** or ***E***. In this setting, I make simplifying assumptions (constant hazard rates over time, allocation 1:1).

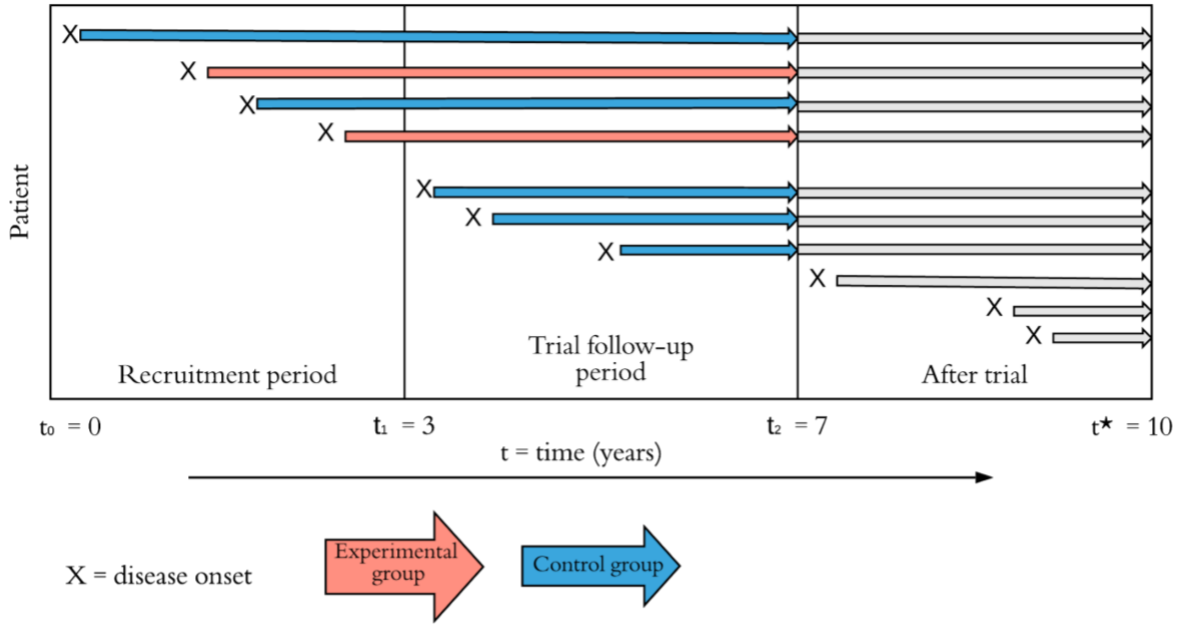

Figure 1. Schematic representation of the timeline of a hypothetical clinical trial.

Research question

The main goal of this thesis is to assess and illustrate how a decision theoretic perspective can be used to optimize a trial design in the setting described above, with a specific focus on trials in an ALS population. In this context, the parameters to be optimized are t_1 and t_2, which determine the **size** and **duration** of the trial.

Primarily, I will focus on maximizing the overall life expectancy in the population by optimizing t_1 and t_2. In addition, I will evaluate the fixed and variable costs and gains associated with the study, as well as the overall probability of drawing a correct conclusion.

By doing so, I hope to provide researchers with a more elaborate perspective on the various consequences of different trial design options. R-code resulting from our evaluation will be provided to enable the procedures to be applied in different contexts.

If time allows, I will look into more complex designs, where the simplifying assumptions mentioned above don't hold [7].

Ethical clearance

Data from ALS trials owned by UMC Utrecht will be used to obtain realistic estimates of e.g. hazards, disease onset rates and plausible effect sizes. Informed consent was formulated broadly so that exploratory analyses can be conducted. Data is already anonymous. No further problems with access to the data are expected, but formal approval still needs to be obtained.

Possible journals for publication:

- Clinical Trials
- Pharmaceutical Statistics
- BMC Medical Research Methodology

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