Statistical Methods for Combining Clinical Trial Phases II And III

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Abstract: This chapter reviews recently developed methodology for designs that combine clinical trial phases II and III in a single trial. The designs enable both selection of the best of a number of experimental treatments and comparison of this treatment with a control treatment, and allow the trial to be stopped early if the best experimental treatment is insufficiently promising or is clearly superior to the control. The stopping rules are constructed to preserve the overall type I error rate for the trial. Two-stage designs are reviewed briefly and two multistage methods based, respectively, on the adaptive and group-sequential approaches are described in detail. The latter are illustrated by a trial to compare three doses of a new drug for the treatment of Alzheimer’s disease.

Keywords and phrases: Adaptive designs, phase II/III trials, select and test designs, sequential clinical trials, treatment selection

26.1 Introduction

In the statistical design of clinical trials to evaluate new drugs, an area of considerable interest is the combination of clinical trial phases II and III into a single trial, because this allows the drug development process to be accelerated. Trial design methods with this aim have been proposed by Thall et al. (1988, 1989), Schaid et al. (1990), Bauer and Kieser (1999), Stallard and Todd (2003), Royston et al. (2003), and Inoue et al. (2002). Their approaches extend the sequential design of clinical trials where two or more interim analyses are conducted as data accumulate through the course of the trial. In essence, the new methods use one or more of the earlier interim analyses to replace the phase II trial. A single trial is thus conducted which allows selection of
one or more of the experimental treatments, as would usually take place in a phase II trial, as well as the comparison of the selected treatment(s) with the control treatment as in a phase III trial. With the exception of Royston et al. (2003) and Inoue et al. (2002), all of the cited papers focus on the construction of frequentist designs in which the overall type I error rate allowing for the treatment selection is controlled. These two papers, however, address a slightly different problem in the combination of phases II and III: that of the use of a definitive endpoint in the final ‘phase III’ analysis and a surrogate endpoint in the interim ‘phase II’ analysis. Royston et al. (2003) propose a frequentist solution to this problem, whereas Inoue et al. (2002) adopt a Bayesian method. Although the use of surrogate endpoints is considered briefly in the Discussion section, most of this chapter is concerned with frequentist methods that allow for treatment selection based on the use of the same endpoint throughout. The chapter provides a review of such methods, illustrating the advantages that their use might bring and highlighting when they are most appropriate. An example of a clinical trial to compare several dose levels of galantamine for the treatment of Alzheimer’s disease is used to illustrate and compare the newer methods and future directions and challenges in this field are discussed.

Following this introductory section, we give an overview of the clinical testing process for a new drug in Section 26.2, explaining the roles played by phase II and phase III clinical trials. The advantages and limitations associated with the combination of phases II and III are then discussed. As several of the methods described rely on statistical methodology for sequential clinical trials comparing a single experimental treatment with a control treatment, a brief summary of this area is given in Section 26.2. The main description of the methods combining phases II and III is given in Section 26.3, together with the illustrative example. We end with a discussion of the methodology and remaining challenges in Section 26.4.

## 26.2 Background

### 26.2.1 The clinical evaluation programme for new drugs

The programme of clinical evaluation of a new drug prior to application to regulatory authorities for registration can be divided into three phases. Phase I clinical trials are small-scale trials in which the first exposure to humans of the new drug is carefully assessed. The focus is on the safety of the drug, and the subjects will often be healthy volunteers. A control group may be included to maintain blindness, but formal comparison between treated and control groups is unusual. A number of doses of the new drug are generally used, with the aim of determining the maximum tolerated dose; the highest