1. Introduction

In general, patients enter a Phase II clinical trial sequentially and hence their responses to the treatment are reported consecutively. Under slow enrollment and long treatment duration, a long observational period is required before information concerning the primary endpoint, such as binary responses, becomes available in the study. For example, liposomal anthracyclines and paclitaxel are considered the best available cytotoxic therapies for Kaposi’s sarcoma (KS), which is the most common malignancy associated with human immunodeficiency virus (HIV) infection, but relapse is common. To identify new interventions for relapsed or progressive KS, a Phase II study of low-dose etoposide to assess its toxicity and efficacy was conducted (Evans et al. [1]). Thirty-six patients were accrued into the study between January 1995 and March 1998 from 11 ACTG centers and were treated with oral etoposide 50 mg/d for 7 consecutive days of every 2-week cycle. The median time to response was 17.7 weeks; the median duration of response was 25 weeks. Hence, the drug development process becomes very long and may delay the release of a promising new drug to the public.

Simon’s two-stage designs [2] are often employed in Phase II clinical trials to avoid giving patient an ineffective drug and described in the following: Among a predetermined number of patients, \( n_1 \), recruited at the first stage, if the number of responses is less than a specified value \( r_1 \), then the trial is stopped. Otherwise, this trial is allowed to continue to the second stage and an additional \( n_2 \) patients is recruited. If the total number of responses is less than a specified value \( r_2 \), then this drug is declared ineffective. Otherwise, this drug is declared effective. Note that the design parameters \( n_1, r_1, n_2 \) and \( r_2 \) are derived based on the binomial distribution under two criteria for selected significant level \( \alpha \) and power \( 1-\beta \).

Based on the stopping rules of Simon’s two-stage design, if the new drug proves ineffective then Simon’s two-stage designs would certainly shorten the drug development process. This design, however, may still require a long observational period for a promising new drug. Herrmann and Szatrowski [3] applied the curtailed sampling procedures studied by many authors, such as Phatak and Bhatt [4], to speed up the development process for drugs in a single-stage clinical trial. More recently, Ayanlowo and Redden [5] apply stochastic curtailment to Simon’s two-stage designs based on conditional power to permit early termination of the trial due to lack of efficacy. Their procedure depends highly on the chosen conditional power threshold \( \gamma \), which is chosen between 0.05 and 1 in order to maintain reasonable power and does not provide stopping rules for early termination in the case of a highly efficacious treatment. Therefore, an alternative curtailed two-stage design, which allows early termination of a trial when a treatment is either very effective or very ineffective, is constructed in the next section.
2. The proposed method

The curtailed sampling procedure is extended to Simon’s two-stage designs in this section. First, the maximum numbers of subjects \( n_1 \) and \( n_1 + n_2 \) required at the first and second stages, respectively, can be derived according to binomial sampling. Similarly, the corresponding cutoff point \( r_1 \) used to determine whether to continue or terminate the trial at the first stage and the critical point \( r_2 \) used to make decision at the second stage are derived in the same way. For example, these design parameters \( n_1, r_1, n_2 \) and \( r_2 \) can be taken from Simon’s two-stage design. In addition, these design parameters can be derived according to some optimality criteria based on the probability structure of the proposed design. Let \( Y_1 \) and \( Y_2 \) be the numbers of subjects needed to make decision at the first stage and second stage, respectively. Then the curtailed two-stage design is described in the following and demonstrated in Figure 1:

At the first stage, among \( Y_1 \) currently enrolled and treated patients with known results,

if \( r_1 \) successes (responses) are first observed, then the trial moves to the second stage, or

if \( n_1 - r_1 + 1 \) failures (non-responses) are first observed, then the drug is declared ineffective, or

if neither of the above cases is observed currently, then the trial continues to recruit patients until it reaches the upper bound \( n_1 \), and then a decision is determined to stop the trial or move to the second stage.

At the second stage, among \( Y_1 + Y_2 \) currently enrolled and treated patients,

if \( r_2 \) successes are observed first, then the null hypothesis is rejected, or
if $n_1 + n_2 + r_2 + 1$ failures are observed first, then the drug is declared ineffective, or

if neither of the above cases is observed, then the trial continues to recruit patients until it reaches the upper bound $n_1 + n_2$, and then a decision is determined to declare effective or ineffective.

To have some feeling about the proposed design, the implementation of the proposed design to an ongoing clinical trial is demonstrated in the next section.

3. Example

To investigate the safety and activity of RT-PEPC (Rituximab, Thalidomide and Metronomic Oral Chemotherapy with Prednisone, Etoposide, Procarbazine and Cyclophosphamide) in recurrent Mantle cell Lymphoma patients, a Simon’s optimal two-stage design has been conducted by Ruan et al. [6] to detect a desirable target response rate of 60% and to a rule out response rate of 40%, with an $\alpha$ value of 0.05 and a $\beta$ value of 0.2. Under this design, the trial terminates early at the first stage if 7 or fewer responses occur in the first 16 patients, otherwise this trial continues to the second stage. While under the curtailed optimal two-stage design, either the trial stops early at the first stage if as early as $n_1 - r_1 + 1 = 9$ non-responses are observed among current enrolled subjects, or this trial moves to the second stage if 8 responses are observed first among current enrolled and treated patients. At the second stage of Simon’s optimal two-stage design, the trial continues to recruit 30 patients and if 23 or fewer responses occur among fixed total number of 46 patients then the treatment is claimed to be ineffective after the second stage, otherwise the treatment is claimed to be effective. Whereas under the curtailed optimal two-stage design, the trial continues to recruit patients and either the treatment is declared to be effective as soon as 24 responses are observed among current enrolled and treated patients or the treatment is declared to be ineffective as early as 23 non-responses are observed.

This RT-PEPC clinical trial is still ongoing since only fourteen patients were enrolled with 11 observed responses. According to Simon’s optimal two-stage design, this trial is still at the first stage, since the number of observed responses is 11 and exceeds the critical point and hence 2 more patients needed to complete the first stage trial. According to the curtailed optimal two-stage design; however, this trial already moves to the second stage because among 11 current treated patients, 8 responses are observed first. Based on the information collected so far, this trial definitely will continue to the second stage and 32 additional patients have to be recruited and treated before making a decision under Simon’s optimal two-stage design. Instead, this trial is expected to be stopped much earlier by applying curtailed optimal two-stage design and the expected total number of patients to be recruited is about 36, which is significantly less than 46.

4. Comparison results

It is interesting to compare expected sample sizes of Simon’s two-stage designs, curtailed two-stage designs and stochastically curtailed Simon’s designs under $p = p_0$. To have some feeling about the expected sample sizes of three designs, based on the parameters of Simon’s two-stage design used in Ayanlowo and Redden [5], the expected sample sizes computed for three designs are listed in Table I. When Simon’s two-stage designs continue to recruit patients until the predetermined number of patients has been treated, under the same design parameters, $n_1$, $r_1$, $n_2$ and $r_2$ the expected total number of patients of Simon’s two-stage design is greater than that of curtailed two-stage design and stochastically curtailed Simon’s designs. When $p_0$ is not too small, the proposed designs compared with stochastically curtailed Simon’s designs have a slight reduction in expected sample size. Moreover, stochastically curtailed Simon’s designs may have a sequence of stopping rules for early termination due to lack of
Drug efficacy at the second stage, while the curtailed two-stage designs provide fixed stopping rules at each stage. Hence, the curtailed two-stage designs are much easier to implement in practice. This confirms that the usefulness and convenience of the proposed design in saving the number of recruited patients and hence experimental time. When drug safety is not a primary concern or the patient accrual is expected to be very slow, the curtailed two-stage designs are recommended to apply in practice to accelerate the process of drug discovery and development.

Table I. Comparison expected sample size of three designs under $p=p_0$.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Simon’s design</th>
<th>Curtailed design</th>
<th>Stochastically curtailed</th>
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<td>$p_0$</td>
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* denotes the conditional power threshold.

References