An optimal stratified Simon two-stage design

Deepak Parashar, a, * Jack Bowden, b Colin Starr, b Lorenz Wernisch, b and Adrian Mander b

In Phase II oncology trials, therapies are increasingly being evaluated for their effectiveness in specific populations of interest. Such targeted trials require designs that allow for stratification based on the participants’ molecular characterisation. A targeted design proposed by Jones and Holmgren (JH) [20] in the context of Phase II cancer trials, which is now briefly described. In the first stage of the JH design, a new therapy is assessed for its activity (its response rate) simultaneously in the biomarker-positive and biomarker-negative sub-populations. The JH design then uses the first stage data to guide whether to (a) continue to study an unselected (biomarker positive and negative) population during the second stage, or (b) enrich the population by enrolling only biomarker-positive subjects. This design has been used in a Phase II study of HER2-negative breast cancer [21]. In Section 2, we discuss the JH design framework in detail. In Section 3, we provide explicit formulae for probabilities of various positive outcomes and extend the JH framework so that error rates can be controlled using several new definitions. In Section 4, we report optimal designs for the various error rate definitions, and we conclude with a discussion in Section 5.

2. SUMMARISING JONES–HOLMGREN DESIGN

The purpose of the Jones–Holmgren (JH) design [20] is to assess the performance of an experimental treatment in a biomarker-negative population, and potentially a biomarker-positive population as well. Let the true response rates for the biomarker-negative and positive (and even adaptive) trial designs aim to estimate a common treatment effect in the disease population. In the realm of stratified medicine, designs are needed to both assess the clinical utility of biomarkers as a diagnostic tool to guide treatment, as well as to estimate a treatment’s effect within each biomarker subgroup. Various designs have been proposed for the biomarker trials, for example biomarker-stratified designs, enrichment designs and the biomarker-strategy designs (10–18). The reader is referred to [19] for a comprehensive review. The execution of biomarker trials often requires interim monitoring and analysis. Therefore, it is natural to set them in the context of an adaptive design. In this paper, we review and extend a biomarker-stratified Simon two-stage design proposed by Jones and Holmgren (JH) [20] in the context of Phase II cancer trials, which is now briefly described. In the first stage of the JH design, a new therapy is assessed for its activity (its response rate) simultaneously in the biomarker-positive and biomarker-negative sub-populations. The JH design then uses the first stage data to guide whether to (a) continue to study an unselected (biomarker positive and negative) population during the second stage, or (b) enrich the population by enrolling only biomarker-positive subjects. This design has been used in a Phase II study of HER2-negative breast cancer [21]. In Section 2, we discuss the JH design framework in detail. In Section 3, we provide explicit formulae for probabilities of various positive outcomes and extend the JH framework so that error rates can be controlled using several new definitions. In Section 4, we report optimal designs for the various error rate definitions, and we conclude with a discussion in Section 5.

1. INTRODUCTION

Group-sequential trial designs, in which the data are periodically assessed to determine whether the trial should continue, can be far more efficient than trials of a fixed sample size. They help in minimising the trials’ duration, cost and number of people exposed to ineffective treatments ([1,2]). The simplest example of an adaptive trial is a two-stage design introduced for Phase II cancer trials by Gehan [3], Fleming [4], Simon [5] and many others ([6,7]). Of particular interest is the Simon two-stage design [5]; it tests a single treatment with a binary response, and an interim analysis is used to allow the trial to stop early for futility only. Simon’s design requires pre-specification of the null response rate, the desired type I error probability and sufficient power at a targeted response rate. Assuming the null hypothesis to be true, their adaptive design uses results from a single interim analysis to decide whether to enrich the study population with a subgroup or not; it is based on two parallel Simon two-stage designs. We study the JH design in detail and extend it by providing a few alternative ways to control the familywise error rate, in the weak sense as well as the strong sense. We also introduce a novel optimal design by minimising the expected sample size. Our extended design contributes to the much needed framework for conducting Phase II trials in stratified medicine. © 2016 The Authors Pharmaceutical Statistics Published by John Wiley & Sons Ltd

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negative and biomarker-positive sub-populations be \( p^- \) and \( p^+ \), respectively. The null hypotheses are \( H_0^- : p^- = p_0^- \), \( H_0^+ : p^+ = p_0^+ \), and the alternative hypotheses are \( H_1^- : p^- > p_0^- \), \( H_1^+ : p^+ > p_0^+ \) where \( p_0^- > p_0^+ \) and \( p_0^+ > p_0^- \). This hypothesis setup implies that any response rate \( p_1 > p_0 \) (i.e. a positive outcome) is considered effective and warrants further study, that is, a go decision, whereas any response rate \( p_1 \leq p_0 \) is considered ineffective and constitutes a no-go decision. While this would be true at the second stage, stopping the study at the first stage as a go-no goes not to be a conclusion of \( p_1 \leq p_0 \) but rather ruling out that the response rate is as good as \( p_1 \). We further fix \( p_0^- = p_0^+ \). This implies that the biomarker is potentially predictive of treatment effect, rather than a prognostic indicator of underlying health. For the particular example trial, they consider \( p_0^- = p_0^+ = 0.03, p_1^+ = 0.15, p_1^- = 0.10 \). An order restriction is assumed for the response rates, namely, \( p^- \leq p_u \leq p^+ \) (i.e. \( p_u \) is the response rate in the unselected population which is a weighted average of the response rates in the biomarker-negative and biomarker-positive sub-populations), and we stick to this assumption in this paper.

At Stage 1, they begin with two parallel studies (Figure 1), one in \( N_1^- \) biomarker-negative participants and one in \( N_1^+ \) biomarker-positive participants (the total sample size of the first stage is \( N_1 = N_1^- + N_1^+ \)). Activity is first assessed in the biomarker-negative sub-population and, if present, continues to Stage 2 recruiting a further \( N_2 \) participants in the unselected population. However, if no activity is indicated in the biomarker-negative sub-population at Stage 1, they then assess activity in the biomarker-positive sub-population and in case of an indication of activity continue to Stage 2 recruiting a further \( N_{2e} \) participants (subscript \( e \) denotes enrichment) in the same sub-population and subsequently test for a positive outcome or a no-go decision.

On the other hand, in the earlier case of recruiting further participants in the unselected population at Stage 2, that is, \( N_2 = N_2^- + N_2^+ \) (where \( N_2^- \) and \( N_2^+ \) are the number of Stage 2 biomarker-negative and biomarker-positive participants, respectively, and JH assuming the prevalence of marker-positive subjects to be 40%), they test for a positive outcome in the biomarker-negative sub-population, and in case of sufficient responders, the treatment is declared effective in the biomarker-negative sub-population. Note that due to the order restriction, the treatment can also be immediately declared effective in the biomarker-positive population, without the need for further testing. If, however, the treatment is ineffective in the biomarker-negative population at Stage 2, they then test for a positive outcome in the biomarker-positive sub-population. Furthermore, let \( X^- = X_1^- + X_2^- \) and \( X^+ = X_1^+ + X_2^+ \). We amend the JH design in that we allow the trial to stop at Stage 1 if the required cumulative response of both stages has already been achieved. It has been shown [23] that a study can stop early for a go decision if it is designed to test a null hypothesis only.

Let \( X_1^- \) and \( X_1^+ \) be the number of responders in Stage 1 for the biomarker-negative and biomarker-positive sub-populations, respectively. When there is no enrichment, let \( X_2^- \) and \( X_2^+ \) be the number of responders in Stage 2 for the biomarker-negative and biomarker-positive sub-populations, respectively. When there is enrichment, let \( X_{2e}^- \) be the number of responders in the biomarker-positive sub-population in Stage 2. The total numbers of responders are defined by adding the corresponding responders in each stage, that is, \( X^+ = X_1^+ + X_2^+ \) and \( X^- = X_1^- + X_2^- \).

![Figure 1](image_url) A schematic for the adaptive enrichment stratified design.
At Stage 1, \( k^+_1 \) and \( k^+_1 \) are the minimum number of responders required for each sub-population, to continue the study. When there is no enrichment, \( k^- \) and \( k^+ \) are the minimum number of responders for each sub-population, to declare positive results. When there is enrichment, \( k^+ \) is then the minimum number of responders for the biomarker-positive sub-population at Stages 1 and 2. All X’s are binomially distributed, and we have that \( k^- \leq k^- \) and \( k^+ \leq k^+ \).

At the end of the study, there are three possible positive trial outcomes: rejecting both null hypotheses and claiming efficacy in the unselected population; rejecting \( H_0 \) and claiming efficacy in the biomarker-positive sub-population without enrichment; and rejecting \( H_0 \) and claiming efficacy in the biomarker-positive sub-population after enrichment. Each of these three outcomes are labelled Routes 1, 2 and 3, respectively, in Figure 1.

Note that it is neither a biomarker stratified design (because of the second stage depending upon rules for the first stage based on activity in biomarker-positive subjects coupled with activity in the biomarker-negative subjects) nor an enrichment design (because the focus is not only biomarker-positive subjects) in the true sense. Instead, it is an adaptive enrichment design that enriches the biomarker-positive participants only adaptively conditional on observing a lack of activity in the biomarker-negative subjects and some activity in the biomarker-positive subjects. The design can be indexed completely by the 10 design parameters

\[
\frac{(k^-_1, k^+_1)}{(N^-_1, N^+_1)} \rightarrow \frac{(k^-_2, N^-_2)}{(N^+_2, k^+_2)} \rightarrow \frac{k^-}{N^-} \rightarrow \frac{k^+}{N^+}
\]

where parameters to the left of the arrow are the Stage 1 thresholds \((k)\) out of the sample sizes \((N)\), while parameters to the right of the arrow are the Stage 2 thresholds out of the respective sample sizes. Therefore, given the aforementioned 10 design parameters together with the response rate probabilities, the study is completely pre-specified and ready to be implemented. This leads to simple rules for making decisions at the interim analysis.

### 3. Calculating the Hypothesis Rejection Probabilities

We now look at the probabilities of rejecting the hypotheses and hence determine the significance and power for the study design. It is important to note that the formulae given in the JH paper [20], Equations (5)–(8) do not take into account the dependence between Stage 1 results and the Stage 2 tests. The probabilities for Stage 2 are conditional upon the number of responders at Stage 1, and so, their product should be summed over \( i \) up to the minimum of \((N^-_1, k^- - 1), (N^+_1, k^+_2 - 1)\) instead of just \(N^-_1, N^+_1\) and so on because the maximum number of responders in Stage 1 will either be the total number of responders at the end of Stage 2 or the numbers recruited at Stage 1, whichever is the minimum. The formulae given here express the conditional probabilities of rejecting the hypotheses in both the sub-populations.

The probability of rejecting both hypotheses \( H_0 \) and \( H^+ \) via Route 1 (Figure 1), that is, declaring a go decision in the unselected population, is

\[
R_1(p^-) = \left( \min(N^-_1, k^- - 1) - i \right) \left( \sum_{i = k^-}^{N^-_1} P(X^+ \geq k^+ - i) P(X^- \geq i) \right) + P(X^- \geq k^-) .
\]

Note that this formula is different from Equation (5) of [20]. The first term of (2) represents the probability that the responders at Stage 2 are greater than or equal to the required responders at Stage 2 conditional on the cut-off responders at Stage 1, with appropriate summation as mentioned earlier. The additional second term in (2) yields the probability that the number of responders at Stage 1 itself is greater than the cumulative responders required at the end of the second stage. Note that \( R_1(p^-) \) is a monotonically increasing function of \( p^- \), the response rate in the negative population, and also that rejecting both null hypotheses does not depend on the response in the positive sub-population.

The probability of rejecting \( H^+ \) via route 2 (Figure 1), that is, declaring a go decision in the biomarker-positive sub-population, is

\[
R_2(p^-, p^+) = P(X^+ \geq k^+) \left( \sum_{i = k^-}^{\min(N^-_1, k^- - 1)} P(X^- \geq i) P(X^+ \geq k^+) \right)
\]

Note that \( R_2(p^-, p^+) \) is a monotonic function of \( p^+ \) but for fixed \( p^- \) the function is not monotonic in \( p^- \) and has a single maximum, a formula for which is given in the Supporting Information.

The probability of rejecting \( H^+ \) via Route 3 (Figure 1), that is, declaring a go decision in the biomarker-positive sub-population with enrichment, is

\[
R_3(p^-; p^+) = P(X^+ \geq k^+ - i) P(X^- \geq i) + P(X^- \geq k^-) \]

Formulae (3) and (4) are also different from Equation (6) of [20], and take into account the conditional probabilities. Equation (4) has an additional term which represents the probability that, for the biomarker-positive sub-population, the number of responders at Stage 1 itself is greater than the required cumulative responders at both stages. Note that \( R_3(p^-, p^+) \) is a decreasing function of \( p^- \) and an increasing function of \( p^+ \). The probability of obtaining a positive result in Equation (2) only depends on the true response rate \( p^- \) in the negative population, while the other routes of obtaining a positive result (via Equations (3) and (4)) depend on the true response rates \((p^-, p^+)\) in both the subgroups.

In order to evaluate these probabilities, we will assume the responders, \( X_i \), follow binomial distributions: \( X^+ \sim B(N^+, p^+) \), \( X^- \sim B(N^-, p^-) \), \( X^+ \sim B(N^+, p^+) \), \( X^+ \sim B(N^+, p^+) \), and so on. From these functions, we can denote the total probability of rejecting \( H^+ \) via Routes 2 or 3 as \( R_3(p^-; p^+) = R_2(p^-, p^+) + R_3(p^-; p^+) \). Also, we can denote the total probability of rejecting at least one null hypothesis as \( R_{123} (p^-; p^+) = R_1(p^-) + R_2(p^-, p^+) + R_3(p^-; p^+) \). Using the pre-specified targeted response rates for each sub-population, \( p^- \) and \( p^+ \), we consider three different scenarios: no efficacy, \( p^-_1, p^+_1 \);
Table I. The probability of each positive outcome at three pre-specified real-world scenarios.

<table>
<thead>
<tr>
<th>Real world</th>
<th>No Efficacy ($p_0^-, p_0^+$)</th>
<th>Outcomes</th>
<th>Reject $H_0^-$ and $H_0^+$</th>
<th>Reject $H_0^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No Efficacy ($p_0^-, p_0^+$)</td>
<td>$R_0 (p_0^-, p_0^+)$ True negative</td>
<td>$R_1 (p_0^-)$ False positive</td>
<td>$R_{23} (p_0^-, p_0^+)$ False positive</td>
<td></td>
</tr>
<tr>
<td>2. Unselected ($p_1^-, p_1^+$)</td>
<td>$R_0 (p_1^-, p_1^+)$ False negative</td>
<td>$R_1 (p_1^-)$ True positive</td>
<td>$R_{23} (p_1^-, p_1^+)$ Wrong positive</td>
<td></td>
</tr>
<tr>
<td>3. Positive only ($p_0^+, p_1^+$)</td>
<td>$R_0 (p_0^+, p_1^+)$ False negative</td>
<td>$R_1 (p_1^-)$ Wrong positive</td>
<td>$R_{23} (p_0^+, p_1^+)$ True positive</td>
<td></td>
</tr>
</tbody>
</table>

Table II. Power, Type I error constraints and the value of $V$ for each design scenario and rejection decision.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Reject $H_0^-$ and $H_0^+$</th>
<th>Reject $H_0^+$</th>
<th>Constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ($p_0^-, p_0^+$)</td>
<td>$R_1 (p^-)$ &amp; $\leq \alpha (2)$</td>
<td>$\leq \alpha (1)$</td>
<td>$\sum \leq \alpha$</td>
</tr>
<tr>
<td>2. ($p_1^-, p_1^+$)</td>
<td>$\geq$ power (0)</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td>3. ($p_0^+, p_1^+$)</td>
<td>$\leq \alpha (1)$</td>
<td>$\geq$ power (0)</td>
<td>$-$</td>
</tr>
</tbody>
</table>

Power is defined as in Equation (5), and the Type I error is given by

$$R_{123} (p_0^-, p_1^+ \leq \alpha).$$

Equation (6) may make it appear that we are only controlling FWER in the weak sense, which is when all null hypotheses are true. However, by doing so, we are also controlling the probability of incorrectly rejecting $H_0^-$ and correctly rejecting $H_0^+$ when $p^- = p_0^-$ and $p^+ = p_0^+$. This is because $R_1 (p^-)$ is independent of the value of $p^+$. Hence, control is also in a strong sense. Note that nothing is specified about controlling the rate of wrong positives and we ignore individual weighting of each positive outcome.

3.3. Expected sample size

Let us now define the expected sample size and the associated optimality criteria for this design. If the trial stops at the first stage, the sample size is $N_1$. If the trial continues to the second stage, then the sample size will either be $N_1 + N_2$ or $N_1 + N_2^+$. The expected sample size is therefore

$$E(N) = N_1 + N_2 p (k^- \leq X^- < k^-) + N_2^+ p (X_1^+ < k_1^-) P \left( \frac{X_1^+}{N_2} \leq \frac{k_1^+}{N_2} \right).$$

(7)

Let $\Omega$ be the set of all designs that satisfy the Type I error constraint and have sufficient power. Then, the optimal design is an element of $\Omega$ that has the smallest expected sample size $E(N)$ under the global null hypothesis $(p^-, p^+) = (p_0^-, p_0^+)$, where $X_1 \sim B \left( N_1, k_1^- \right)$ and $X_1^+ \sim B \left( N_1^+, k_1^- + 1, p^+ \right)$. Formula (7) now takes into account early stopping for efficacy. The overall probability of early termination PET is given by the formula

$$PET = P \left( X_1^+ \geq k^+ \right) + P \left( X_1^+ < k_1^- \right) \left[ P \left( X_1^+ \geq k_1^+ \right) + P \left( X_1^+ < k_1^- \right) \right].$$

(8)

4. RESULTS

We now present the results for the operating characteristics due to JH, as well as our new optimal designs.
In the previous section, we have already explained what we mean by optimal designs. A point to note is that Simon’s optimal design is under the assumption that the null hypothesis is true. Of late, there has also been interest in generating optimal design strategies under the alternative hypothesis [23–25]; however, we shall not delve into this aspect in the current paper. Note that the expected sample sizes obtained in Table III are not optimal. This is in contrast to our method for obtaining the designs where we choose the one with the smallest expected sample size and present the associated design parameters. Table IV below gives optimal designs for various different sets of the targeted response probabilities and controlling the FWER. The null hypotheses set \( p_0^\pm = 0.03 \).

## 4.1. Jones–Holmgren tables revisited

In Table III, we show the route probabilities (corresponding to power and Type I error rates calculated using Formulae (2)–(4)) and expected sample sizes for the same parameter constellations as in Table I of Jones and Holmgren [20]. Note that the power in the biomarker-positive sub-population differs when calculated using our formulae. We also explicitly give the expected sample sizes, both due to the two parallel Simon two-stage design \( E(N)_{\text{Simon}} \) (defined in Appendix A of [20]) as well as the adaptive design \( E(N)_{\text{Adaptive}} \).

For power, let us consider the targeted response rates \( p_1^+ = 0.15, p_1^- = 0.10 \) from Table III. The probability of rejecting both hypotheses (i.e. Route 1) is 75.5%, which is the same as that obtained by JH. Now, the probability of rejecting \( H_0^+ \) (i.e. Routes 2 and 3) is quoted in JH as 17.5% making the overall power of 93% as per their definition (Equations (7) and (8) of [20]) of adding these rejection probabilities at different response rates. However, using the formulae as described in the preceding section yields a probability of 72%, and we claim the power of their design is therefore 72% (the minimum of the two rejection probabilities), that is, less than the desirable 80%.

In the next subsection, we exhibit the optimal designs obtained using the formulae given in the previous section.

## 4.2. Optimal designs

In the previous section, we have already explained what we mean by optimal designs. A point to note is that Simon’s optimal design is under the assumption that the null hypothesis is true. Of late, there has also been interest in generating optimal design strategies under the alternative hypothesis [23–25]; however, we shall not delve into this aspect in the current paper. Note that the expected sample sizes obtained in Table III are not optimal. This is in contrast to our method for obtaining the designs where we choose the one with the smallest expected sample size and present the associated design parameters. Table IV below gives optimal designs for various different sets of the targeted response probabilities and controlling the FWER. The null hypotheses set \( p_0^\pm = 0.03 \).

The optimal designs were calculated by an exhaustive search over the 10-dimensional design parameter space. This space is very large, containing up to \( 10^{17} \) possible designs for the larger trials needed for low-targeted responses. To make the computation tractable, the search space was pruned wherever possible, using strictly logical (i.e. non-heuristic). For example, the power in the unselected population can be calculated using only four parameters, and if the power is too small, we do not need to iterate over the remaining six. This can reduce the search space by perhaps three orders of magnitude, depending on the parameters.

The program was run using a Graphics Processing Unit, or GPU, similar to the graphics card in many high-end computers. A GPU contains several hundred small processors and is suitable for massively parallelisable problems, like this one, where each possible design can be calculated in parallel. The GPU provides a gain in speed of between 5 times and 50 times, depending on the parameters used. These techniques reduced the program execution time to between 30 s and 24 h, with the longer times required when the expected sample size (and hence the search space) was large. The maximum size of the search space needs to be configured by the user, but it is easy to set a search space sufficiently larger than the proposed optimal design to be confident that it is indeed the true optimum. The code is available at

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Table III. Operating characteristics given the design (2 1)/(34 14) → (5/50) | (4 4)/(53 27).

<table>
<thead>
<tr>
<th>( p_1^- )</th>
<th>( p_1^+ )</th>
<th>( R_1(p_1^-) )</th>
<th>( R_{23}(p_0^\pm, p_1^+) )</th>
<th>( E(N)_{\text{Simon}} )</th>
<th>( E(N)_{\text{Adaptive}} )</th>
<th>( E(N)<em>{\text{Adaptive}} / E(N)</em>{\text{Simon}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>0.03</td>
<td>0.067</td>
<td>0.012</td>
<td>74.61</td>
<td>65.79</td>
<td>0.881</td>
</tr>
<tr>
<td>0.03</td>
<td>0.10</td>
<td>0.067</td>
<td>0.424</td>
<td>85.21</td>
<td>76.91</td>
<td>0.902</td>
</tr>
<tr>
<td>0.03</td>
<td>0.15</td>
<td>0.067</td>
<td>0.720</td>
<td>88.36</td>
<td>80.21</td>
<td>0.907</td>
</tr>
<tr>
<td>0.10</td>
<td>0.15</td>
<td>0.755</td>
<td>0.720</td>
<td>127.66</td>
<td>80.03</td>
<td>0.626</td>
</tr>
<tr>
<td>0.10</td>
<td>0.25</td>
<td>0.755</td>
<td>0.905</td>
<td>129.78</td>
<td>80.44</td>
<td>0.619</td>
</tr>
<tr>
<td>0.15</td>
<td>0.30</td>
<td>0.952</td>
<td>0.924</td>
<td>136.99</td>
<td>80.10</td>
<td>0.584</td>
</tr>
</tbody>
</table>

\( p_0^\pm = p_0^+ = 0.03 \), Significance, \( \alpha = 0.079 \)

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Table IV. Optimal designs — controlling FWER at 5% and setting \( p_0^\pm = p_0^+ = 0.03 \).

<table>
<thead>
<tr>
<th>( p_1^- )</th>
<th>( p_1^+ )</th>
<th>Significance</th>
<th>( R_1(p_1^-) ) (unselected)</th>
<th>( R_{23}(p_0^\pm, p_1^+) ) (positives)</th>
<th>PET</th>
<th>( E(N) )</th>
<th>Optimal design</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>0.10</td>
<td>0.048</td>
<td>0.800</td>
<td>0.800</td>
<td>0.623</td>
<td>110.2</td>
<td>( (3/44 34) \rightarrow (7/104)</td>
</tr>
<tr>
<td>0.10</td>
<td>0.15</td>
<td>0.049</td>
<td>0.801</td>
<td>0.801</td>
<td>0.653</td>
<td>77.9</td>
<td>( (2/2)/(32 21) \rightarrow (6/67)</td>
</tr>
<tr>
<td>0.10</td>
<td>0.25</td>
<td>0.050</td>
<td>0.800</td>
<td>0.800</td>
<td>0.571</td>
<td>60</td>
<td>( (2 1)/(34 8) \rightarrow (42 29)</td>
</tr>
<tr>
<td>0.15</td>
<td>0.15</td>
<td>0.050</td>
<td>0.802</td>
<td>0.801</td>
<td>0.611</td>
<td>46.9</td>
<td>( (2 1)/(20 12) \rightarrow (43 6)</td>
</tr>
<tr>
<td>0.15</td>
<td>0.25</td>
<td>0.046</td>
<td>0.803</td>
<td>0.802</td>
<td>0.561</td>
<td>32.5</td>
<td>( (1 1)/(12 7) \rightarrow (42 28)</td>
</tr>
<tr>
<td>0.15</td>
<td>0.35</td>
<td>0.045</td>
<td>0.801</td>
<td>0.800</td>
<td>0.615</td>
<td>27.8</td>
<td>( (1 1)/(11 5) \rightarrow (3 15)</td>
</tr>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.045</td>
<td>0.802</td>
<td>0.801</td>
<td>0.695</td>
<td>18.5</td>
<td>( (1 1)/(6 6) \rightarrow (3 24)</td>
</tr>
<tr>
<td>0.25</td>
<td>0.40</td>
<td>0.038</td>
<td>0.802</td>
<td>0.801</td>
<td>0.742</td>
<td>13.5</td>
<td>( (1 1)/(6 4) \rightarrow (2 9)</td>
</tr>
</tbody>
</table>
the weblink http://www.mrc-bsu.cam.ac.uk/published-research/additional-material/.

The designs in Table IV have been obtained by fixing the significance level to be at most 5% and power to be at least 80%. Comparing the example trial $p^+ = 0.15$, $p^- = 0.10$ used by JH from Table III with $E(N)_{\text{Simon}} = 127$, we find that our optimal designs for these response rates offer a substantial efficiency in terms of the expected sample sizes of 78. According to our definition, this design also has a smaller expected sample size than the design suggested by Jones and Holmgren that had insufficient power. Our designs yield even smaller expected sample sizes as we increase the desired response rates to be much higher than the null response rates of 3%. All across Table IV, the probability of declaring a go decision for the unselected population at Stage 1 remains very low with $P(\chi^2 \geq k^-) = 5.04 \times 10^{-4}$ being the maximum.

The rejection probability functions are plotted in Figure 2 for the design from the first row of Table IV, $(3/2)/(44 34) \rightarrow (7/104) | (9/4)/(135 53)$. As shown earlier, the function $R_1(\cdot)$ is non-monotonic in $p^-$ but monotonic in $p^+$. Using our design-finding software, one can obtain a plethora of optimal designs by varying the null and the desired response rate probabilities. A selection of these is available at the aforementioned URL.

5. DISCUSSION

In this article, we have taken the design of Jones and Holmgren and provided alternative definition of power and choice of Type I error controls. Additionally, we introduce an extension of their work to provide designs that are optimal, in the sense that we are minimising the expected sample size. A selection of optimal

![Figure 2. The rejection probabilities for each route.](image)

<table>
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<th>Table V. Comparison summary of JH and our work</th>
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<td>Adaptive enrichment with futility stopping</td>
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<td>Rejection probabilities not conditional on Stage 1 results</td>
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Underlying assumptions common to both: $\rho_0 = \rho_0^+$ (no prognostic effect), $\rho^- \leq \rho_1^+$ (order restriction)

JH, Jones and Holmgren.
designs are provided in the Supporting Information including the computer code to create any design required. We demonstrated that our optimal design was more efficient than Jones and Holmgren's original, and also it gave a 60% reduction in the expected sample size compared to the parallel Simon two-stage design. Table V summarises our work against that of Jones and Holmgren.

The underlying assumption $\alpha_0 = \alpha^+$ may signify that there is no prognostic effect. Because a trial design cannot distinguish a prognostic biomarker from a predictive one, we assume that the biomarker is predictive. However, the biomarker could be prognostic too, but we have not attempted to evaluate this. The optimal designs obtained in our paper are, however, robust to deviations from this assumption because in our programme code one can a priori specify the different values of $\alpha_0$ and $\alpha^+$.

Another major assumption of the Jones and Holmgren design is the order restriction on the parameter space, that is, the response for the biomarker-positive sub-population is bigger than in the biomarker-negative sub-population. One implication of this is when the $H_0^+$ hypothesis is rejected then both are rejected without using the information in the biomarker-positive sub-population, which represents an inefficient use of the data. Another, more fundamental issue is that even if expert scientific opinion suggest biomarker status rigidly dictates treatment response, the assumption could be wrong. Note that if the order restriction is relaxed then an additional wrong positive error may occur. This is the case of only rejecting $H_0^+$ for the additional scenario of an effect in the negative subgroup only ($p_1, p_2$).

It is widely known that single-arm trials may be subject to selection bias and any treatment response being due to the patient population rather than the effect of treatment. Additionally, for the stratified single-arm trials, a positive result might mean that the biomarker is a prognostic biomarker rather than a predictive biomarker. A randomised trial will be needed to confirm predictive ability; however, a single-arm trial is much smaller and could be valuable within a drug development plan. Recent literature [26–28] on single-arm trials in oncology continues to provide early indication of effectiveness of the interventional drug, for example, in the evaluation of cytotoxic treatment resulting in tumour reduction. Given that the goal of single-arm trials is hypothesis testing, they screen out ineffective drugs quickly and cheaply. Such trials are also of benefit where the goal is to prioritise which, if any, experimental regimen should progress to a go/no-go decision and a go decision, respectively. However, we cannot have such inequalities in our alternative hypotheses for the stratified design because of the reasons of non-monotonicity mentioned previously.

When obtaining our optimal designs, we did not attempt to control the rate of wrong positives, and we ignored the individual weighting of each positive outcome. Of course, one may wish to do so. In the Supporting Information, we discuss several alternative methods of error control and present alternative tables of optimal designs that flow from them. This is available at the aforementioned URL.

It might not be possible to plan the enrolment of precise numbers of biomarker-positive and of biomarker-negative participants. In future work, we plan to expand our algorithm to compute optimal designs providing overall sample sizes only without the need to find fixed number of biomarker-positive or negative samples. Effectively, the algorithm needs to integrate out all possibilities of biomarker-positive and negative sample sizes given an overall size. Because our algorithm is combinatorial in nature, essentially enumerating all possible scenarios, such integration can be easily incorporated. That is, given a fixed prevalence rate in addition to the other parameters described earlier, the algorithm will provide a design not in terms of biomarker-positive and negative sample sizes but overall sample sizes. Such extension is easily incorporated by keeping track of modified expected sample size calculations based on the binomial distribution using the biomarker prevalence rate. A branch and bound approach for small probability regions of the combinatorial space will allow us to cut down the search space.

A subtle point is that absolute fulfilment of false positive and false negative constraints can no longer be guaranteed. If only total sample sizes are given, even with non-extreme biomarker prevalence rates, low numbers of biomarker-positive or negative sample sizes with high error rates are possible, if unlikely. However, exploiting the low probability of such cases, guarantees can be provided for the proposed designs to breach error rate constraints with only a small and user defined probability.

REFERENCES

D. Parashar et al.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher’s web site.