Sequential, Adaptive, and Enrichment Strategies

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Despite substantial progress in the prevention of cardiovascular disease and its ischemic complications, it remains the single largest killer in the United States. New treatment options are needed, particularly to respond to the challenges of an aging population and rising rates of obesity and diabetes. Development of novel therapeutic strategies for the management of acute cardiovascular disease is especially challenging. Specific problems include relatively low event rates, diverse patient populations, lack of reliable surrogate end points, and small treatment effects subject to substantial uncertainty. Because the clinical development process is enormously expensive and time consuming, there is considerable interest in statistical methods that use accumulating data from a clinical trial to inform and modify its design. Such redesign might include changes in target sample size and even changes in the target population. This article discusses developments in adaptive design of interest to cardiovascular research.

To illustrate the methods we discuss, we focus on the development of novel therapies for the management of acute coronary syndromes. However, the ideas we discuss have much wider application. We begin by discussing the traditional approach to determination of a fixed sample size for a clinical trial. We then describe group sequential designs and the benefit they provide in the conduct of trials. In the section on Adaptive Sample Size Reestimation, we discuss designs that are adaptive in the sense that they allow an adjustment of the target sample size based on the accumulating data from the trial. In the section on Adaptive Sample Size Reestimation With Enrichment, we discuss enrichment designs that shift the focus to a patient subgroup when the accumulating data suggest greatest benefit for that subgroup. Additional details about population enrichment are provided in the online-only Data Supplement.

The Setting

We consider therapies intended to reduce the risk of acute ischemic complications in patients undergoing percutaneous coronary intervention. For specificity, we consider a placebo-controlled randomized trial with a composite primary end point including death, myocardial infarction, or ischemia-driven revascularization during the first 48 hours after randomization. We assume, based on prior knowledge, that the placebo event rate is in the range of 7% to 10%. The investigational drug is assumed, if effective, to reduce the event rate by 20%, but the evidence to support this assumption is limited. The actual risk reduction could be larger but could also easily be as low as 15%, a treatment effect that would still be of clinical interest given the severity and importance of the outcomes, but that would require a substantial increase in sample size. As is often true when clinical trials are planned, there is substantial uncertainty about both the placebo-group event rate and the treatment effect. In the following sections, we describe how 4 design strategies perform in such situations. We assume throughout that patients are randomized in equal proportions to the experimental and placebo arms. Because the primary objective is to determine whether the new treatment is superior to placebo, our focus will be on 1-sided hypothesis testing.

Fixed Sample Size Designs

The simplest and most common method for determining sample size in the presence of uncertainty is to take best estimates, sometimes based on limited information, of both the placebo group event rate and the treatment effect, apply one of the standard sample size formulas, and perform a fixed sample size trial with that target enrollment. Suppose that \( \pi_0 \) represents the event rate for the placebo arm, \( \pi_t \) the event rate for the experimental arm, and \( \rho = (\pi_t/\pi_0) \) the relative risk in the treatment and control groups. We are interested in testing the null hypothesis, \( H_0 \), that the event rates do not differ in the treatment and placebo arms \( (\rho = 1) \). If we employ a 1-sided level-\( \alpha \) test, the combined sample size \( N \) (both arms) needed to achieve power \( 1 - \beta \) to reject the null hypothesis when \( \rho \) is <1 is

\[
N = 2 \left[ \frac{1 - \rho \pi_0}{\rho \pi_0} + \frac{1 - \pi_t}{\pi_t} \right] \left( z_{1-\beta} + z_{1-\alpha} \right)^2 / \ln(\rho)
\]

where \( z_{1-\beta} \) and \( z_{1-\alpha} \) are the appropriate percentiles of the standard normal distribution. For example, when \( \pi_0 = 8\% \), the com-

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/119/4/597/DC1.

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(Circulation. 2009;119:597-605.)

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.108.809707
Combined sample size needed to detect a 20% risk reduction (i.e., a relative risk of $\rho=0.8$) with 80% power with a 1-sided level-0.025 test is calculated from Equation 1 as $N=8236$.

This approach has 2 important limitations: The power varies as a function of both the placebo group event rate and the magnitude of the treatment effect. For instance, if $\pi_c=7\%$ instead of 8%, the sample size needed to detect a 20% risk reduction with 80% power increases from $N=8236$ to $N=9503$. If, in addition, the actual risk reduction is only 18%, the required sample size increases even further to $N=11 841$. Figure 1 displays the power of an 8000-patient study for 3 different placebo-group event rates and risk reductions between 15% and 22%, in which the risk reduction is 100(1-$\rho$)%. The power of the study varies from 53% to 93%. In subsequent sections, we focus on the middle curve, corresponding to an 8000-patient fixed sample trial with an 8.7% placebo-group event rate. For this event rate and a relative risk of $\rho=0.8$, 8000 patients yield power of 82%.

When we design a trial with a fixed sample size based on an assumed placebo-group event rate and treatment effect, we are at risk of mounting a trial that is underpowered for the actual situation. When the end point is measured as the time to the event rather than the event rate, the dependence of power on prior knowledge of the placebo-group event rate can be eliminated by continuing the trial to a prespecified number of events, $D$. The number of events needed for a 1-side level-$\alpha$ test to detect a hazard ratio $\rho$ with 1-$\beta$ power is then given by

$$D = 4 \left( \frac{z_\alpha + z_\beta}{\ln(\rho)} \right)^2$$

(See, for example, Rao and Schoenfeld.1) Unlike Equation 1, Equation 2 does not depend on the control group event rate.

When the end point is binary, that is, the occurrence or nonoccurrence of the event rather than the time to the event, the event-driven approach does not eliminate dependence of sample size on the control group event rate. Event-driven trials are, however, a special case of a more general approach for trial design known as the information-based design. In an information-based design, the statistical information rather than the sample size is fixed in advance. The trial continues to enroll patients until the desired amount of statistical information is attained. Prior specification of $\pi_c$ at the design stage is thereby eliminated. The information-based approach is described in greater detail in the online-only Data Supplement and elsewhere.2

Neither event-driven trials nor their generalization to information-based trials is helpful when the treatment effect is different than anticipated at the planning stage. If it is smaller than anticipated, the study can fail even though the investigational drug is beneficial. If it is larger than anticipated, the study can enroll more patients than would have been needed to demonstrate superiority of the new drug. In the remainder of this article we discuss more flexible group sequential and adaptive designs, as well as enrichment strategies, that address both the uncertainty about the placebo-group event rate and the uncertainty about the treatment effect.

**Group Sequential Designs**

By the 1960s, investigators recognized both the risk of ignoring trends and the risk of responding too quickly to trends observed in comparisons of treatment groups during the course of an ongoing trial. Seminal articles by Pocock3 and O’Brien and Fleming4 described statistical methods for determining critical values that could be used to analyze accumulating data at a fixed number of prespecified occasions. These group sequential designs permit early stopping for efficacy based on interim analyses of the accumulating data without inflating the false-positive rate, also known as the type 1 error rate. The O’Brien-Fleming group sequential designs have been used widely because they are more
conservative than other designs in early analyses and therefore reduce the risk of stopping early on the basis of a strong trend based on limited experience. Lan and DeMets\textsuperscript{5} introduced the idea of an \( \alpha \) spending function that allows Data and Safety Monitoring Boards to modify the timing of interim analyses based on logistical and other considerations, while preserving \( \alpha \), the allowable type 1 error. Formally, an \( \alpha \) spending function is an increasing function of sample size that specifies the cumulative type 1 error that may be expended at any interim analysis time point. It assumes the value 0 at sample size 0 and the value \( \alpha \) at the maximum sample size, thereby ensuring that the overall type 1 error of the trial cannot exceed \( \alpha \).

Group sequential designs provide a framework that allows Data and Safety Monitoring Boards to stop trials early when a sufficiently strong trend is observed without compromising the statistical strength of the evidence. One can also build in futility stopping rules for terminating a trial if interim results suggest that a positive outcome would be unlikely\textsuperscript{6} if the trial were continued. To achieve the same power for a given treatment effect, studies with an interim analysis plan must have a larger maximum sample size than the fixed sample size design, but the expected sample size, accounting for the gain achieved by early stopping, will typically be smaller for sequential designs than for fixed sample size designs.

To illustrate, consider a group sequential design with interim analyses after 50\% and 70\% of patients are enrolled, making a total of 3 analyses (including the final analysis). Using standard group sequential software,\textsuperscript{7,8} one can show that an O’Brien-Fleming design with an overall one sided type 1 error of 0.025 would achieve statistical significance at the first look if the nominal 1-sided probability value was \(<0.0015\), would achieve statistical significance at the second look if the nominal 1-sided probability value was \(<0.0069\), and would achieve statistical significance at the third and final look if the corresponding nominal 1-sided probability value was \(<0.0227\). In contrast, a single (final)-look level-0.025 design would achieve statistical significance if its nominal 1-sided probability value at the end of the study was 0.025.

Now suppose that we add a futility stopping rule whereby the trial will be terminated early if the interim results are trending in the wrong direction. Any reasonable futility rule can be imposed because early stopping for futility cannot inflate the type 1 error rate. Stopping for futility will, however, decrease power because it increases the chances of a false-negative outcome. To offset this power loss, one must increase the sample size of the group sequential design. Suppose, for example, that we decide to terminate for futility at the first interim analysis if the estimated risk of an event is 1\% greater for the experimental treatment than for placebo, and at the second interim analysis if the conditional power (or probability of a successful outcome at the end of the trial given the current data and assuming that the current estimate of the treatment effect is the true effect in the population) is <20\%. Suppose also that the placebo-group rate is 8.7\%. In that case, Figure 2 shows that, to match the power curve of the 8000-patient fixed sample size design, the maximum sample size of the 3-look group sequential design must be increased to 8750 patients.

Having equated the power curves of the fixed sample and group sequential designs, we can compare the 2 designs with respect to average sample size. Figure 3 displays average sample sizes for different values of percent risk reduction over the relevant range. The average sample size for the fixed sample design is constant throughout with \( N=8000 \). Although the group sequential design requires an upfront commitment of \( N_{\text{max}}=8750 \) patients, its average sample size is substantially lower because of the possibility of early stopping. The average sample size of the group sequential design ranges between 6400 and 7000 patients, achieving smaller expected sample size than the fixed sample size design by \( \approx1000 \) patients when the risk reduction with the investigational drug is \( \approx15\% \) and by \( \approx1600 \) patients when the risk reduction is \( \approx22\% \).

Figure 2. Power curves for the fixed sample-size design with \( N=8000 \) and the group sequential design with \( N_{\text{max}}=8750 \).
Group sequential designs can produce efficiency gains relative to fixed sample size designs, and they also protect patients when the treatment effect is larger than expected because stronger trends will lead to earlier termination. They do not, however, help in the situation in which the investigational drug is beneficial but with an effect size smaller than that assumed in the initial study design; in this circumstance, the only useful action is a substantial increase in the sample size, a decision that is typically based on financial and logistical considerations.

### Adaptive Sample Size Reestimation

Many modern trials in cardiovascular disease require large international networks of investigators and substantial initial investments. The coordination of these trials is complex and resource intensive. Moreover, these phase 3 (or confirmatory) trials come at the end of an already long and costly drug development process. Although the study is initially designed with a particular effect size in mind (say 20%), the drug may be of clinical interest when the effect size is somewhat smaller (say 15%), and investigators may wish to increase the sample size rather than carry on with an underpowered trial when the accumulating data suggest that the effect size is smaller than anticipated. Until recently, statisticians believed that use of accumulated data to modify the trial design would compromise the statistical integrity of the trial. In an important article, however, Müllner and Schäfer9 showed that, at any interim analysis, a group sequential design can be modified to change the number and timing of subsequent analyses without altering the unconditional type 1 error rate, provided that the conditional type 1 error of the modified design is identical to the conditional type 1 error of the original design. The conditional type 1 error of either design is defined as the probability of rejecting the null hypothesis when it is in fact true, given the accumulated data at that analysis point and continuation of the trial according to the original or modified design.

Intuitively, if the conditional type 1 error of the study is preserved by the modified design for every realization of the data, it must be preserved for the study as a whole, and therefore the overall type 1 error is preserved. Thus, if the original interim analysis plan had a type 1 error rate of 0.025, a plan that allows for redesign of the sequential boundary but satisfies the Müller and Schäfer condition will also have a type 1 error rate of 0.025.

The implications of this observation are enormous. If, at an interim analysis, the accumulated data yield a point estimate of effect size that is half the size of the effect employed in the initial study, the investigators have the option of increasing the sample size to achieve desired power against this smaller effect. Of course, this may be impractical or the effect may not be of clinical interest. Still, this represents an important new dimension in trial design that is critical to consider given the complexity and cost of performing large international clinical trials.

To illustrate the Müller and Schäfer principle, consider once again the 8750 patient 3-look group sequential design described in the previous section. This design is displayed schematically in Figure 4. The $x$ axis shows the sample size at each of the three looks, and the $y$ axis shows the corresponding efficacy and futility boundaries on the standardized normal scale. To be specific, let $\hat{p}_i$ denote the estimate of the relative risk, $p$, and $N_j$ be the combined sample size at look $j$ for $j = 1, 2, 3$. Then the standardized test statistic at look $j$ is computed as

$$Z_j = \frac{\ln(\hat{p}_j)}{\text{se}[\ln(\hat{p}_j)]}$$

where se[ln($\hat{p}_j$)] is the standard error of ln($\hat{p}_j$) and is estimated by the formula.
Parameter values on a large sample size, they are good estimates of the true 8.7% at the second look. Because these estimates are based /H11015 estimated event rate for the control arm, is 266/3026, or /H11015 beyond the second look. The estimate of the relative risk at /H11015 either the efficacy or futility boundaries, the trial can continue /H11015 power curve displayed in Figure 2 shows that the unconditional power of this study is only /H11015 calculate the conditional power or probability that at the final /H11015 hypothesis that the treatment and placebo arms have equal /H11015 Wald statistic, Z1, as the Wald statistic. Under the null hypothesis that the treatment and placebo arms have equal risk, the Wald statistic has a standard normal distribution.

Figure 4 shows that at the first look, when N1=4375, the trial stops for efficacy if Z1≤−2.96 and for futility if Z1≥0.1. At the second look, when N2=6125, the corresponding efficacy and futility bounds for Z2 are −2.46 and −1.29, respectively. At the final look, when N3=8750, the null hypothesis is rejected in favor of the active treatment if Z3≤−2.0. Otherwise, the null hypothesis is accepted. The unconditional type 1 error, or probability that the Wald statistic will cross one of the efficacy boundaries under the null hypothesis, is 0.025 for this group sequential design.

Example
Now consider a hypothetical trial in which the data at the first and second looks are displayed in the Table. Because the test statistics, Z1=−1.6728 and Z2=−1.8816, do not exceed either the efficacy or futility boundaries, the trial can continue beyond the second look. The estimate of the relative risk at the second look is ̂p2. That is, the estimated percent risk reduction is only 15.07%. The Table also reveals that ̂π2, the estimated event rate for the control arm, is 266/3026, or ≈8.7% at the second look. Because these estimates are based on a large sample size, they are good estimates of the true parameter values ρ and πc, respectively. For these values, the power curve displayed in Figure 2 shows that the unconditional power of this study is only ≈58%. We can also calculate the conditional power or probability that at the final look the Wald statistic, Z3, will drop below −2.0, conditional on the observed value of Z2=−1.8816 and assuming that ρ=̂p2 and πc=̂π2. This probability is only 67%. Thus, by either assessment the trial is underpowered.

We can increase power by increasing the sample size. Suppose we wish to increase the conditional power from 67% to 80%. With the use of Equation 6 of Gao et al, the final sample size must be increased from 8750 patients to 10 678 patients to achieve this power. However, because the sample size modification is based on the data observed at the second interim analysis, we must invoke the Müller and Schäfer criterion at the final analysis to protect the overall type 1 error. This means that the conditional type 1 error, or conditional probability of a statistically significant outcome under the null hypothesis, given Z2, must remain the same for the altered and unaltered trials. The conditional type 1 error of the unaltered trial is depicted in Figure 5 as the probability, under the null hypothesis, that the sample path will drop below −2.0 and thereby enter the efficacy zone at the final look. We have calculated this probability to be 0.22.

Figure 6 depicts the altered trial with a sample size of 10 678 patients. For the conditional type 1 error of the altered trial to also be 0.22, the final critical value must be increased from −2.0 to −1.93. Because the original design had an unconditional type 1 error of 0.025, an adaptive trial in which the conditional type 1 error is preserved will also have an unconditional type 1 error of 0.025.

When an adaptive trial is to be implemented, we recommend that the decision rules for making the adaptive change be prespecified and evaluated by simulation. Accordingly, suppose we decide in advance that we will, if necessary, increase the sample size of the original 3-look group sequen-

Table. Data at Looks 1 and 2 of a 3-Look Group Sequential Trial

<table>
<thead>
<tr>
<th>Look</th>
<th>Sample Size N</th>
<th>Control Event Rate ̂πc</th>
<th>Experimental Event Rate ̂πc</th>
<th>Relative Risk ̂ρ</th>
<th>Log Relative Risk ln(̂ρ)</th>
<th>Standard Error se[ln(̂ρ)]</th>
<th>Wald Statistic Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4375</td>
<td>190/2187 (8.68%)</td>
<td>160/2188 (7.31%)</td>
<td>0.8417</td>
<td>−0.1731</td>
<td>0.103</td>
<td>−1.6728</td>
</tr>
<tr>
<td>2</td>
<td>6125</td>
<td>266/3062 (8.69%)</td>
<td>226/3063 (7.38%)</td>
<td>0.8493</td>
<td>−0.1633</td>
<td>0.0868</td>
<td>−1.8816</td>
</tr>
</tbody>
</table>

Figure 4. Stopping boundary for the group sequential design with N=8750 and type 1 error=0.025 (1-sided).
tial design at the second interim analysis so as to achieve 80% conditional power against an alternative hypothesis equal to the estimated effect size at that analysis. Specifically, after completing the second interim analysis and concluding that the trial should not be stopped for either superiority or futility, we perform a sample size reestimation (subject to a cap) based on the observed effect size. If the conditional power of the study can be increased to 80% for that effect size with a revised total sample size of <15,000, the sample size will be increased to that number. If the power is <80% for a sample size of 15,000, the sample size will be left at the originally specified 8750. This latter feature is not required but establishes a cap on the maximum sample size. The cap reflects consideration of the clinical importance of an assumed effect size, the operational challenges of additional patient recruitment, and the financial limitations of the required enrollment.

The power curve for this adaptive group sequential design can be evaluated by simulation and is displayed in Figure 7 alongside the power curve for the nonadaptive group sequential design with a maximum sample size of 8750 patients and the 8000-patient fixed sample design. The adaptive group sequential design produces a power gain of 3% to 4% across the range of effect sizes of interest.

Figure 8 displays the expected sample sizes for the 3 designs. Both the group sequential and adaptive group sequential designs achieve a substantial reduction in average sample size compared with the fixed sample design. Moreover, even though it was permissible for the sample size of the adaptive group sequential design to increase to as much as 15,000 patients, the average sample size is in the range of 6600 to 7400 patients because of the presence of the efficacy and futility boundaries. We also note from Figure 8 that the

Figure 5. Status of the group sequential design at the second interim analysis. The conditional type 1 error is 0.22.

Figure 6. Boundaries for the modified group sequential design that preserves the conditional type 1 error at 0.22 and also has power of 0.80 against the effect size observed at the second interim analysis.
3% to 4% gain in power relative to the nonadaptive group sequential design is achieved at the cost of between 200 and 400 additional patients on average.

Adaptive sample size reestimation will not be appropriate for every situation. It could result in recommendations for substantially larger trials, possibly to pursue effect sizes of limited clinical interest. Thus, it is a tool to be applied judiciously. However, in settings in which a sponsor has made a substantial investment and the investigators find that the apparent effect size, while smaller than initially planned, is still clinically important, it can provide another path to a positive result without compromising the integrity of the trial.

**Adaptive Sample Size Reestimation With Enrichment**

In some clinical settings, there is reason to believe that the treatment effect might vary among patient subgroups. For example, an intervention might provide greater benefit to patients with comorbid conditions based on the pathophysiology of their disease and the mode of action of the pharmacological agent studied. In such situations, one might like to have an option to enrich the patient population, that is, to selectively enroll the remainder of the patients in the subgroup(s) in which greatest benefit is observed at the interim look.

**Example**

Let \( G_0 \) denote the entire population under study. Suppose that investigators have identified 2 subgroups of patients, \( G_1 \), and \( G_2 \), such that \( G_1 \) is a subset of \( G_0 \) and \( G_2 \) is a subset of \( G_1 \). Let \( H_i \) denote the null hypothesis that the treatment and control arms are equally efficacious in population \( G_i \), for \( i = 0, 1, 2 \).

We now describe a design that allows both sample size reestimation and enrichment after an interim analysis.

We assume as before that the initial target sample size is 8750 patients and that interim analyses will be performed at 50% and 70% of that target. We also assume that the sample size reestimation at the 70% mark will first be attempted without enrichment, as described in the section Adaptive Sample Size Reestimation, so as to achieve 80% conditional power with the \( G_0 \) population. However, if the sample size reestimation for \( G_0 \) produces a revised sample size >15,000,
we will consider enrichment. The enrichment strategy proceeds as follows: We first estimate the number of additional patients needed to test the null hypothesis $H_1$ with 80% conditional power, assuming that the observed effect size in $G_1$ is the true effect size. That is, we consider testing for a treatment effect in the $G_1$ subpopulation. If that sample size plus the number of patients already enrolled is $< 15,000$, the trial will continue until the additional number of patients is enrolled, but future eligibility will be restricted to patients belonging to subgroup $G_1$. If that enrichment strategy does not yield a sample size $< 15,000$, the same calculation will be performed with the estimated effect size for subgroup $G_2$ and, if that reestimation yields a sample size $< 15,000$, the trial will continue, enrolling only members of $G_2$. If neither of the sample size calculations for the patient subgroups yields a sample size $< 15,000$, the trial will be continued with the original eligibility criteria and sample size target, provided that the conditional power with 8750 patients is at least 20%. Otherwise, the trial will be terminated for futility.

A question arises as to how to test for a treatment effect at the end of the trial given the possibility of a sample size increase and population enrichment at the second interim look. To preserve the type 1 error of the study as a whole, we employ a closed testing procedure that guarantees strong control of the type 1 error rate. Specifically, if enrichment is implemented, the testing procedure involves 2 hypothesis tests. Suppose for specificity that the data lead to an enrichment strategy and patients enrolled from $G_1$ thereafter. This test is based on the original adaptive design, so the group sequential boundaries and the Muller and Schäfer procedure ensure that test 1 will be a level-α test. However, if test 1 rejects the null hypothesis, we can conclude only that the new treatment is superior to placebo in either the $G_0$ population or the $G_1$ subpopulation. Thus, we then perform test 2, a conventional level-α test of the null hypothesis $H_2$ in patients from the $G_1$ subpopulation enrolled after the second interim analysis, that is, after enrichment began. If both hypotheses are rejected, we conclude that treatment is superior to placebo in the $G_1$ subpopulation. A similar procedure is followed if enrichment is limited to subgroup $G_2$.

Details of this testing procedure and the demonstration that it provides strong control of type 1 error are provided in the online-only Data Supplement.

### Simulation Experiments to Investigate Population Enrichment

Investigators conducting a large clinical trial comparing a novel antithrombotic agent with clopidogrel in patients undergoing percutaneous coronary intervention partitioned the overall patient population into 4 mutually exclusive subpopulations in which the event rates were expected to differ. The 4 subpopulations were as follows:

- **High-risk patients pretreated with clopidogrel ($\approx 30\%$ of study population)**
- **Low-risk patients naive to clopidogrel ($\approx 20\%$ of study population)**
- **Low-risk patients pretreated with clopidogrel ($\approx 20\%$ of study population)**

In this classification, high-risk patients are those with diabetes or an elevated troponin level. These subpopulations were selected before any unblinding of the data on the following basis:

1. They were clinically relevant and easily identifiable in a clinical setting.
2. Current understanding of the underlying pathophysiology supported the hypothesis that the risk reduction with the study drug relative to clopidogrel might differ in the 4 subpopulations.
3. Parameters to identify the subpopulations were consistently collected.

For purposes of population enrichment, the aforementioned 4 subpopulations were combined into 3 nested groups $G_0$, $G_1$, and $G_2$ as follows:

- **$G_0$, the entire group**
- **$G_1$, the subgroup of high-risk patients ($60\%$ of $G_0$)**
- **$G_2$, the subgroup of high-risk patients naive to clopidogrel ($50\%$ of $G_1$)**

To evaluate the adaptive enrichment strategy for selecting $G_0$, $G_1$, or $G_2$ at the second interim look, we generated events from the 4 mutually exclusive subpopulations, consolidated them according to the definitions of the 3 nested groups, and implemented the group sequential, sample size increase, and enrichment rules outlined in the earlier sections of this article. Because there are infinitely many ways to specify response rates for the treatment and control arms, we limited our investigation to 2 scenarios: a case of heterogeneous risk reduction across the 4 subpopulations and a case of homogeneous risk reduction across the 4 subpopulations. As before, we assume a 3-look group sequential trial with a planned maximum sample size of 8750 patients, interim looks after 50% and 70% of enrollment, and the possibility of increasing the sample size to 15,000 patients at the second interim analysis. The rules for enrichment and the subsequent hypothesis tests for strong control of type 1 error are as specified in the previous section. We provide a brief summary of the findings here. The results are discussed in greater detail in the online-only Data Supplement.

### Scenario 1: Heterogeneous Risk Reduction

We considered a scenario in which the average risk reduction for the $G_0$ population was 17.4% but the 2 nested subgroups benefited to a greater extent than the average patient, with a risk reduction of 22.6% for $G_1$ and 27.1% for $G_2$. In this heterogeneous setting, the overall chance of claiming treatment efficacy for either $G_0$, $G_1$, or $G_2$ is boosted by enrichment from 69% to 81%. This 12% gain in power is achieved at the cost of an average sample size increase of 840 patients.
and a 3% drop in the chance of claiming efficacy for G₀ alone, relative to a design with no enrichment.

Scenario 2: Homogeneous Risk Reduction

We considered a scenario in which the G₀, G₁, and G₂ populations all achieved the same risk reduction of 17.4%. In this homogeneous setting, the enrichment design produces a 5% gain in power, from 69% to 73%. This 5% gain in power is achieved at the cost of an average sample size increase of 366 patients and a 1% drop in the chance of claiming efficacy for G₀ alone relative to a design with no enrichment.

In any application of the enrichment strategy, simulation results should be explored extensively because they enable the trial leadership to weigh the tradeoffs between an overall power gain, an increase in average sample size, and the possibility that, at the end of the trial, efficacy may only be claimed for a subset of the G₀ population.

Conclusions

As we have demonstrated, adaptive and enrichment designs for phase 3 trials are feasible and methodologically sound. Considerable work and practical experience, however, will be needed to characterize how best to use these designs in clinical research.

Although we have described the enrichment component of the study design in terms of prespecified subgroups, the 2-stage testing procedure has the advantage of allowing the group responsible for redesign to choose any patient subgroup on the basis of analysis of the accumulating data or external information. Because the null hypothesis of equal efficacy in the enriched subgroup is tested only in patients enrolled after the second interim analysis, the null distribution of that test does not depend on the procedure or deliberations used to define the subgroup. Narrowing patient eligibility to a subgroup is not without cost, of course, because more restrictive eligibility criteria make it more difficult to enroll patients and will usually require an extension of the enrollment period. Of course, any potential labeled indication for a drug or device might then be restricted to the enriched subgroup. Thus, enrichment designs must be studied carefully before they are applied in any specific trial.

Disclosures

Dr Bhatt discloses the following relationships: research grants (directly to the institution): Bristol-Myers Squibb, Eisai, Ethicon, Heartscapte, Sanofi Aventis, The Medicines Company; consultant/advisory board (donated to nonprofits for >2 years): Arena, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Cardax, Centocor, Co- genus, Daiichi-Sankyo, Eisai, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, McNeil, Medtronic, Millennium, Molecular Insights, Otsuka, Paringenix, PDL, Philips, Portola, Sanofi Aventis, Schering Plough, Scios, Takeda, The Medicines Company, Vertex. Dr Harrington discloses the following relationships: research grants to DCRI from The Medicines Company. A full listing of his disclosures is available at http://www.dcri.duke.edu/research/coi.jsp. Dr Ware discloses the following relationships: consultant/advisory board (compensation paid directly to the Harvard School of Public Health): Biogen Idec, The Medicines Company, Schering Plough. Dr Mehta is the President of Cytel Inc, a software and services company whose products and services are used by pharmaceutical and biotechnology companies. He does not derive any personal consulting income from these activities.

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Key Words: statistics ■ clinical trials ■ methods ■ design ■ angioplasty
Optimizing Trial Design: Sequential, Adaptive, and Enrichment Strategies
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Circulation. 2009;119:597-605
doi: 10.1161/CIRCULATIONAHA.108.809707
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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A Note on Information Based Designs

Statistical (or Fisher) information is a technical term referring to the precision with which the treatment effect is estimated. In the present setting the treatment effect, expressed on the logarithmic scale, is \( \ln(\rho) \). The amount of statistical information about \( \ln(\rho) \) is estimated by the square inverse standard error of the estimate of \( \ln(\rho) \). (A formula for \( \text{se}[\ln(\hat{\rho})] \) was provided in Section 5.) On the other hand the total amount of statistical information required to achieve power of \( 1 - \beta \) with a one-sided level-\( \alpha \) test is determined at the design stage to be

\[
I = \left[ \frac{Z_{\alpha} + Z_{\beta}}{\ln(\rho)} \right]^2 \tag{A1}
\]

The trial proceeds to enroll patients until the attained information, \( \text{se}[\ln(\hat{\rho})]^{-2} \), equals the required information, \( I \). In this approach the sample size, \( N \), is increased until a pre-determined amount of information, \( I \), has been attained. Notice that equation (A1), unlike equation (1), does not require knowledge of \( \pi_c \). Therefore in an information based design, prior knowledge of the placebo event rate is not required. For a detailed discussion of information based designs refer to Mehta and Tsiatis (13).

A Testing Procedure that Guarantees Strong Control of Type 1 Error

A valid testing procedure must guarantee strong control of the Type 1 error rate. Strong control implies, that no matter what configuration of null hypotheses is true, the family-wise error rate will be controlled at level \( \alpha \). Table 1S lists all possible null hypotheses and the Type 1 errors that can arise when they are true. The testing procedure is said to achieve strong control of Type 1 error at level \( \alpha \) if the probability of an incorrect conclusion is no greater than \( \alpha \), no matter which row of Table 1S represents the true state of nature.
Marcus, Peritz and Gabriel\textsuperscript{10} have shown that, to achieve strong control of Type 1 error, one must use a \textit{closed testing procedure}. In our setting, to claim statistical significance at level $\alpha$ for any individual null hypothesis $H_i$, one must test and reject $H_i$ at level $\alpha$ \textbf{and in addition} one must test and reject each of the intersection hypotheses listed in column 1 of Table 1S that contains $H_i$, also at level $\alpha$.

The testing procedure described below is closed, and therefore guarantees strong control of the Type 1 error rate. We consider two cases of hypothesis testing – with and without population enrichment.

\textbf{Case 1: Population Enrichment not Implemented}

In this case, a level $\alpha$ test of the hypothesis $H_0$ will be performed on the combined data from the $G_0$ population at the final analysis. The possible sources of inflation of the Type 1 error for this test are the interim monitoring for early stopping, possibly combined with a sample size increase. The group sequential stopping boundaries and the Müller and Schäfer procedure ensure, however, that the Type 1 error will be preserved. The procedure is closed since if $H_0$ is rejected at level $\alpha$ it follows automatically that the intersection hypotheses $H_0 \cap H_1$, $H_0 \cap H_2$ and $H_0 \cap H_1 \cap H_2$ are also rejected at level $\alpha$.

\textbf{Case 2: Population Enrichment Implemented}

Suppose the study has been enriched at the second interim analysis by restricting enrollment to subgroup $G_i$. In this case, two tests will be performed at completion of the trial. Test 1 will be performed first on the entire study population. Since the population enrolled in a trial with enrichment consists of a mix of patients who were enrolled from $G_0$ through the second interim analysis and were subsequently enrolled from $G_i$, Test 1 will be a test of the intersection null hypothesis $H_0 \cap H_i$; i.e., both $H_0$ and $H_i$ are true. The group sequential boundaries and the Müller and Schäfer procedure ensure that Test 1 will be a level $\alpha$ test. Test 1 performs a gatekeeper function. If the null hypothesis $H_0 \cap H_i$ is not rejected, the trial is considered to have produced a statistically non-significant result and no further testing is necessary. However if Test 1 does reject the intersection null hypothesis, all that can be concluded is that the new treatment is
superior to placebo in either the $G_0$ population or $G_i$ subgroup. Test 2, a conventional level test of
the null hypothesis $H_i$, is then performed on the subset of patients from subgroup $G_i$ who were
enrolled after the second interim analysis. The gatekeeper strategy of only performing Test 2 if
Test 1 rejects its null hypothesis ensures strong control of the Type 1 error since it can now be
easily established that $H_i$, and all intersection hypotheses containing $H_i$ are rejected at level $\alpha$.

Simulation Experiments to Investigate Population Enrichment

In Section 7 of the main paper we described a simulation experiment to investigate the benefits
of population enrichment under heterogeneous and homogeneous risk reduction scenarios.
Details of the simulation results are provided below.

Scenario 1: Heterogeneous Risk Reduction

Table 2S displays plausible event rates for the treatment and control arms under a heterogeneous
risk reduction scenario. The column of average event rates weights the event rate of each sub-
population by its size. Table 3S consolidates these response rates into corresponding event rates
for the three nested groups. Results of 100,000 simulated trials are displayed in Table 4S.

Adding the enrichment option boosts the overall power by 12%, from 69% to 81%, under this
configuration of event rates. This gain in power is achieved at the cost of an increase of 840
patients in the average sample size. If there were no enrichment, the investigators would have a
69% chance of claiming treatment efficacy with the entire population $G_0$ whereas under
enrichment the chance of claiming treatment efficacy with $G_0$ is 66%. The simulation allows the
trial leadership to weigh the trade-off between an overall power gain of 12% and a 3% loss in the
probability of claiming treatment efficacy with $G_0$.

A power curve for the enrichment design under heterogeneous risk reduction is displayed in
Figure 1S, alongside the previously computed power curves. The points on this power curve
were obtained by simulating trials in which the vector of clopidogrel event rates was preserved
as in Table 2S, but the vector of event rates for the treatment arm in Table 2S was multiplied by
appropriate factors so as to obtain risk reductions between 15% and 30% for the $G_0$ population.
The enrichment strategy can boost power by 5% to 15%. A corresponding curve of expected
sample sizes is displayed in Figure 2S and shows that these gains in power come at the cost of larger expected sample sizes that range between 250 and 1000 patients.

**Scenario 2: Homogeneous Risk Reduction**

Tables 5S and 6S display plausible event rates and risk reductions for the treatment and control arms under a homogeneous risk reduction scenario. The marginal event rates for the control and treatment arms, 8.7% and 7.2%, respectively, are identical to those in Scenario 1. Consequently the overall percentage risk reduction, 17.4%, is also identical to that of Scenario 1. In Scenario 2, however, the 17.4% risk reduction is constant across G0, G1, and G2, as can be seen from Table 7. Results of 100,000 simulated trials are displayed in Table 7S.

Under a homogeneous risk-reduction scenario, there is about a 5% gain in power if the enrichment option is enabled. The average sample size is increased by 366 patients and the chance of claiming treatment efficacy with the full population G0 is about 1% lower with the enrichment option enabled. Overall it appears that use of the enrichment option is a good insurance policy against the risk of under-powering a large trial involving thousands of patients.
Table 1S: All possible true null hypotheses and corresponding incorrect conclusions

<table>
<thead>
<tr>
<th>True Null Hypothesis</th>
<th>Type of Incorrect Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_0 \cap H_1 \cap H_2$</td>
<td>Treatment is declared superior to placebo in either $G_0$ or $G_1$ or $G_2$</td>
</tr>
<tr>
<td>$H_0 \cap H_1$</td>
<td>Treatment is declared superior to placebo in either $G_0$ or $G_1$</td>
</tr>
<tr>
<td>$H_0 \cap H_2$</td>
<td>Treatment is declared superior to placebo in either $G_0$ or $G_2$</td>
</tr>
<tr>
<td>$H_1 \cap H_2$</td>
<td>Treatment is declared superior to placebo in either $G_1$ or $G_2$</td>
</tr>
<tr>
<td>$H_0$</td>
<td>Treatment is declared superior to placebo in $G_0$</td>
</tr>
<tr>
<td>$H_1$</td>
<td>Treatment is declared superior to placebo in $G_1$</td>
</tr>
<tr>
<td>$H_2$</td>
<td>Treatment is declared superior to placebo in $G_2$</td>
</tr>
</tbody>
</table>

Table 2S: Plausible Event Rates under Heterogeneous Risk Reduction

<table>
<thead>
<tr>
<th>Event Rates</th>
<th>High Risk + Naive to Clopidogrel</th>
<th>High Risk + Pre-treated with Clopidogrel</th>
<th>Low Risk + Naive to Clopidogrel</th>
<th>Low Risk + Pre-treated with Clopidogrel</th>
<th>Average Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel event rate</td>
<td>12%</td>
<td>9%</td>
<td>7%</td>
<td>5%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Experimental drug event rate</td>
<td>8.8%</td>
<td>7.5%</td>
<td>6.6%</td>
<td>5.0%</td>
<td>7.2%</td>
</tr>
<tr>
<td>%Risk Reduction</td>
<td>27.1%</td>
<td>16.6%</td>
<td>6.2%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

Table 3S: Event Rates and Risk Reduction in Nested Groups, Consolidated from Table 2S

<table>
<thead>
<tr>
<th>Group</th>
<th>Representation in Study</th>
<th>Event Rates $\pi_c$</th>
<th>$\pi_e$</th>
<th>% Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G_0$</td>
<td>100%</td>
<td>8.7%</td>
<td>7.2%</td>
<td>17.4%</td>
</tr>
<tr>
<td>$G_1$</td>
<td>60%</td>
<td>10.5%</td>
<td>8.1%</td>
<td>22.6%</td>
</tr>
<tr>
<td>$G_2$</td>
<td>30%</td>
<td>12.0%</td>
<td>8.8%</td>
<td>27.1%</td>
</tr>
</tbody>
</table>
Table 4S: Results of 100,000 Simulations Under Scenario 1

<table>
<thead>
<tr>
<th>Enrichment Option</th>
<th>Prob(Select Group G_i and Win)</th>
<th>Overall Power</th>
<th>Average Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Win with G_o</td>
<td>Win with G_1</td>
<td>Win with G_2</td>
</tr>
<tr>
<td>Not Enabled</td>
<td>69%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Enabled</td>
<td>66%</td>
<td>8%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Table 5S: Plausible Event Rates under Homogeneous Risk Reduction

<table>
<thead>
<tr>
<th></th>
<th>High Risk + Naive to Clopidogrel</th>
<th>High Risk + Pre-treated with Clopidogrel</th>
<th>Low Risk + Naive to Clopidogrel</th>
<th>Low Risk + Pre-treated with Clopidogrel</th>
<th>Average Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel event rate</td>
<td>12.0%</td>
<td>9.0%</td>
<td>7.0%</td>
<td>5.0%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Experimental drug event rate</td>
<td>9.9%</td>
<td>7.4%</td>
<td>5.8%</td>
<td>4.1%</td>
<td>7.2%</td>
</tr>
<tr>
<td>%Risk Reduction</td>
<td>17.4%</td>
<td>17.4%</td>
<td>17.4%</td>
<td>17.4%</td>
<td>17.4%</td>
</tr>
</tbody>
</table>

Table 6S: Event Rates and Risk Reduction in Nested Groups, Consolidated from Table 5S

<table>
<thead>
<tr>
<th>Group</th>
<th>Representation in Study</th>
<th>Event Rates</th>
<th>% Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>π_e</td>
<td>π_e</td>
<td></td>
</tr>
<tr>
<td>G_0</td>
<td>100%</td>
<td>8.7%</td>
<td>7.2%</td>
</tr>
<tr>
<td>G_1</td>
<td>60%</td>
<td>10.5%</td>
<td>8.7%</td>
</tr>
<tr>
<td>G_2</td>
<td>30%</td>
<td>12.0%</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

Table 7S: Results of 100,000 Simulations Under Scenario 2

<table>
<thead>
<tr>
<th>Enrichment Option</th>
<th>Prob(Select Group G_i and Win)</th>
<th>Overall Power</th>
<th>Average Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Win with G_o</td>
<td>Win with G_1</td>
<td>Win with G_2</td>
</tr>
<tr>
<td>Disabled</td>
<td>69%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Enabled</td>
<td>68%</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1S. Power curves for the fixed sample size, group sequential, adaptive, and enrichment designs (heterogeneous case)

Figure 2S. Average sample sizes for the fixed sample size, group sequential, adaptive, and enrichment designs (heterogeneous case)
Figure 1S. Power curves for the fixed sample size, group sequential, adaptive, and enrichment designs (heterogeneous case)
Figure 2S. Average sample sizes for the fixed sample size, group sequential, adaptive, and enrichment designs (heterogeneous case)