Influence of Adaptive Analysis on Unnecessary Patient Recruitment: Reanalysis of the RATPAC Trial

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Study objective: Recruitment to clinical trials is a challenging but essential activity in emergency medicine. Conventional fixed-sample trials may continue to recruit patients after efficacy has been demonstrated or when further recruitment is futile. Adaptive trials make use of emerging information to modify aspects of a trial or terminate it prematurely, potentially resulting in savings in terms of sample size, time, and cost. We aim to use sequential testing procedures to reanalyze data from a fixed-sample trial, the Randomised Assessment of Treatment Using Panel Assay of Cardiac Markers (RATPAC) trial, and investigate the potential for adaptive designs to reduce unnecessary recruitment.

Methods: The trial was reanalyzed with a triangular group sequential design, with interim analyses planned every 3 months. Patients were analyzed in the order in which they entered the original trial.

Results: We found that the RATPAC trial could potentially have stopped 1 year earlier, with 722 patients enrolled compared with 2,243 patients in the original trial, making a potential saving of approximately $390,000. Estimates of effect were similar, and the qualitative conclusions of the original and group sequential RATPAC trials were in agreement. However, the group sequential approach is not without limitations and would have resulted in less precise estimates of effect and less information available for the subsequent evaluation of secondary endpoints.

Conclusion: Sequential designs are well suited in emergency medicine because of the rapidly obtained outcomes and the need to avoid unnecessary recruitment. We recommend that group sequential designs be considered for clinical trials in emergency medicine. [Ann Emerg Med. 2012;60:442-448.]

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INTRODUCTION

Background

A "conventional" clinical trial follows a fixed-sample design, in which features of the trial are prespecified and remain unaltered throughout the trial. The data are analyzed once the trial is complete, with no statistical analyses performed while the trial is ongoing. In this article, we will consider adaptive designs. The Food and Drug Administration defines an adaptive clinical trial as follows:

"A study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. Analyses of the accumulating study data are performed at prospectively planned time points within the study, can be performed in a fully blinded manner or in an unblinded manner, and can occur with or without formal statistical hypothesis testing."[1]

There are many different types of adaptive design. One of the most common designs used in adaptive clinical trials is a group sequential design, which allows trials to be stopped prematurely because of efficacy (demonstration of effect), futility (low likelihood of demonstrating an effect), or safety, according to the results of interim analyses.[2] Interim inspections are planned either after certain numbers of patients have been recruited or at particular points during the study. In the present article, an example is provided in which group sequential methodology is applied to a clinical trial in emergency medicine. A reanalysis is undertaken with data from the Randomised Assessment of Treatment Using Panel Assay of Cardiac Markers (RATPAC) study conducted by Goodacre et al.[3] The RATPAC trial was a multicenter randomized

Editor's Capsule Summary

What is already known on this topic

Group sequential trial designs use accumulated information to stop clinical trials early when there is overwhelming evidence of efficacy, futility, or harm.

What question this study addressed

How results and conclusions with a group sequential design to reanalyze the RATPAC study compare with the original fixed-sample design and how practical this approach is for emergency medicine clinical trials.

What this study adds to our knowledge

The reanalyzed results were comparable to the original, and the study could have been stopped 1 year earlier by enrolling 722 patients compared with 2,243 patients in the original study.

How this is relevant to clinical practice

This methodology is appropriate for some emergency medicine clinical trials and potentially provides study results sooner than traditional fixed-sample designs.

controlled trial in which a new, rapid method of blood testing was compared with the cardiac troponin test currently in use for the diagnosis of acute myocardial infarction in cases of acute chest pain. Six centers participated in the trial, recruiting a total of 2,243 patients during an 18-month period. The primary endpoint was the proportion of patients successfully discharged after assessment, with a successful discharge defined as one in which the patient had been discharged within 4 hours of arrival and experienced no adverse events during the subsequent 3-month period. The 4-hour limit was considered important because at the time of the study the UK had in place a national target of discharging patients from the emergency department (ED) within 4 hours of arrival.

Importance

Clinical trials are essential to developing the evidence base for emergency medicine, but patient recruitment is often difficult. Recruitment typically relies on active engagement of clinical staff, but failure to maintain enthusiasm in the face of competing priorities can lead to failure to achieve recruitment targets. Clinical trials in emergency medicine often require extensions of time and cost to complete recruitment, which may act as a disincentive to future funding. Ensuring that clinical trials in emergency medicine are not unnecessarily prolonged is therefore important to maintain clinical engagement and the support of funding organizations.

It could be argued from an ethical perspective that it is essential that clinical trial data be monitored and adaptations or premature termination be allowed to ensure that participants are not unnecessarily exposed to inferior, ineffective, or unsafe interventions. In the event of no difference between interventions, designs that allow early termination for futility mean that time may be saved and resources reallocated to other promising interventions. For trials with a sufficiently large positive effect from the offset, early stopping or altered allocation ratios mean the new intervention may be exploited sooner and fewer participants receive an inferior intervention. Similarly, early detection of a significant detrimental effect reduces patients' exposure to an inferior intervention and allows the next promising intervention to be evaluated sooner. Group sequential methods offer potential savings in terms of sample size, time, and cost compared with conventional, fixed-sample methods, potentially resulting in more efficient studies.[4]

Goals of This Investigation

In the present study, the RATPAC study was redesigned and analyzed as a group sequential trial to compare the characteristics, results, and conclusions with the original, fixed-sample trial. The aim was to investigate the effects of running the study as a group sequential trial both to assess the practicalities of such designs and to quantify any possible biases caused by stopping early. The intention was to carry forward any acquired knowledge into the design and analysis of future trials. The reanalysis was assisted by having complete trial results for the RATPAC study, enabling an assessment of any potential biases compared with the overall estimate of effect.

MATERIALS AND METHODS

Study Design

Something to consider when designing group sequential trials is when to schedule interim analyses. There are 2 main approaches to scheduling an interim analysis: either after a certain number of participants have been recruited or after a certain amount of calendar time has passed. Some advantages and disadvantages to each approach are outlined in Table 1. For the reanalysis of RATPAC, interim analyses were scheduled to take place every 3 months, allowing a realistic schedule for the independent data monitoring committee and sufficient time between analyses for data to accrue.

It is beyond the scope of the present article to review different adaptive designs because the main aim of this article is to highlight the utility of the adaptive approach in general. For an overview of different adaptive methods, there are many good articles and texts, such as the Food and Drug Administration draft guidance for industry,[1] the review by Chow and Chang,[5] or articles by the PhRMA Working Group on Adaptive Designs (a list of references can be found at http://www.biopharmnet.com/doc/doc12004-01.html; accessed March 6, 2012). The comprehensive texts by Jennison and Turnbull[4] and Whitehead[6] provide particular focus on group sequential methods.

For the present example, the triangular design originally proposed by Whitehead and Stratton[7] was selected because it is