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A Review of Clinical Trials With an Adaptive Design and Health Economic Analysis

Laura Flight, MMath, MSc1,*, Fahid Arshad1, Rachel Barnsley, BSc1, Kian Patel1, Steven Julious, BSc, MSc, PhD1, Alan Brennan, BSc, MSc, PhD2, Susan Todd, BSc, MSc, PhD3

1Medical Statistics Group, School of Health and Related Research, University of Sheffield, Sheffield, England, UK; 2Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, England, UK; 3Department of Mathematics and Statistics, University of Reading, Reading, England, UK

ABSTRACT

Objective: An adaptive design uses data collected as a clinical trial progresses to inform modifications to the trial. Hence, adaptive designs and health economics aim to facilitate efficient and accurate decision making. Nevertheless, it is unclear whether the methods are considered together in the design, analysis, and reporting of trials. This review aims to establish how health economic outcomes are used in the design, analysis, and reporting of adaptive designs. Methods: Registered and published trials up to August 2016 with an adaptive design and health economic analysis were identified. The use of health economics in the design, analysis, and reporting was assessed. Summary statistics are presented and recommendations formed based on the research team’s experiences and a practical interpretation of the results. Results: Thirty-seven trials with an adaptive design and health economic analysis were identified. It was not clear whether the health economic analysis accounted for the adaptive design in 17/37 trials where this was thought necessary, nor whether health economic outcomes were used at the interim analysis for 18/19 of trials with results. The reporting of health economic results was suboptimal for the (17/19) trials with published results. Conclusions: Appropriate consideration is rarely given to the health economic analysis of adaptive designs. Opportunities to use health economic outcomes in the design and analysis of adaptive trials are being missed. Further work is needed to establish whether adaptive designs and health economic analyses can be used together to increase the efficiency of health technology assessments without compromising accuracy. Keywords: adaptive design, cost-effectiveness, clinical trials, value of information

Introduction

Decision makers such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom, the Canadian Agency for Drugs and Technologies in Health, or the Pharmaceutical Benefits Advisory Committee in Australia require high-quality evidence of both clinical effectiveness and cost-effectiveness when making funding recommendations.1-3 Faced with mounting ethical pressures and limited budgets, increasing the efficiency of clinical trials research is a priority.4

Adaptive Designs

Adaptive designs use data collected as a clinical trial progresses to inform modifications to the trial, without compromising the validity or integrity of the study.5 They have the potential to benefit patients and healthcare providers ethically and financially and are becoming a popular alternative to the traditional fixed sample size trial in appropriate clinical circumstances.7,8 Table 1 summarizes some adaptive design methods available. In addition, Chow and Chang provide a comprehensive summary of adaptive designs,14 and Pallmann et al give real-world examples.17

The analysis following an adaptive design requires careful consideration and it is important to account for the adaptive nature of the study design. For example, when a group sequential design (GSD) stops early the analysis may be biased.9 This has the potential to influence a health economic analysis that relies on an accurate estimate of the treatment effect and its associated confidence interval. Further problems may arise when the health economic outcomes, such as costs and quality of adjusted life years (QALY), are correlated with the primary outcome.11

* Address correspondence to: Laura Flight, MMath, MSc, School of Health and Related Research (ScHARR), University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, United Kingdom.
E-mail: l.flight@sheffield.ac.uk
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Health Economics

The methods of economic evaluation facilitate the comparison of the costs and benefits of alternative technologies to determine which is the most cost-effective. Value of information analysis (VOIA) methods assess whether it is worthwhile collecting further information to inform a decision. Table 1 provides a summary of key terms in health economic analyses; Drummond et al provide a comprehensive summary.

Table 1 – Glossary of key terms in the adaptive designs and health economics literature

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
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| Group Sequential Design (GSD) | Interim analyses are carried out after groups of patients have reached the outcome of interest. The trial can stop early if there is sufficient evidence of safety, efficacy, or futility. The analysis following a GSD requires careful consideration because of potential bias introduced by the stopping rules. Methods exist to adjust for this bias in the treatment effect estimate and its confidence interval as well as correlated secondary outcomes.

| Sample Size Re-estimation | The sample size calculated before the trial commenced is updated using information collected up to the interim analysis. This can be conducted blind to the treatment allocation or unblind. A blinded sample size re-estimation does not require any statistical adjustment; nevertheless, when unblinded data are used, the probability of making a type I error increases. Generally, these methods are recommended only to increase the sample size.

| Adaptive Randomisation | Modifications to the randomization procedure after the trial has commenced can be made based on the allocation of previous participants in the trial. This can increase the probability of success of the trial and allow new participants to receive the most promising treatment.

| Internal Pilot | Internal pilots are usually undertaken to assess the feasibility of the trial as opposed to the feasibility of the intervention. Decisions regarding whether a trial should progress are usually made in the context of recruitment or retention rates within the trial. There could also be an opportunity to re-estimate the sample size.

| Multi-Arm Multi-Stage | Multi-Arm Multi-Stage (MAMS) trials allow multiple treatments to be compared with a single control arm. The multiple stages (interim analyses) increase efficiency by allowing arms to be dropped for futility or even for the whole trial to stop if efficacy can be demonstrated.

| Expected Value of Perfect Information (EVPI) | The expected value of perfect information (EVPI) considers the scenario where further research would eliminate all decision uncertainty, representing the most that can be gained from further research. The EVPI can take only positive values; it is potentially worthwhile conducting further research if the associated costs are less than the EVPI.

| Expected Value of Partially Perfect Information (EVPPi) | It may not be feasible to collect further information about all the parameter inputs in a health economic analysis. Instead, the expected value of partially perfect information (EVPPi) can be calculated using the same idea as the EVPI calculation.

| Expected Value of Sample Information (EVSI) | The methods of EVPI and EVPPi estimate the value of eliminating all or an element of uncertainty in a decision problem. It is not, however, always possible to do this. It may be more feasible to consider the value of reducing some of the uncertainty, for example, by conducting another clinical trial or continuing with an adaptive design when presented with interim data. The expected value of sample information (EVSI) can be used to determine the value of a specific research design that will be used to inform a decision.

| Economic Evaluation | “Comparative analysis of alternative courses of action in terms of both their costs and consequences.”

Methods

Data Sources and Search Strategy

To identify a diverse and representative sample of adaptive designs, six sources were used:

1. clinicaltrials.gov—a new review by this research team that involves looking for trials with an adaptive design registered from 2011 onward (accessed August 19, 2016).
2. Peer-reviewed journals via MEDLINE, EMBASE, Cochrane Library, and Web of Science—a new review aiming to identify articles reporting the methods for health economic analysis of adaptive designs. Any articles reporting a clinical trial with an adaptive design were included in the current review.
3. Hatfield et al—reviewed 158 registered clinical trials on clinicaltrials.gov between 2000 and 2014 and the National Institute for Health Research (NIHR) register and contacted experts for known adaptive designs.
4. Stevely et al—reviewed the reporting of 68 published clinical trials using a GSD identified on MEDLINE for years 2001 to 2014.
5. Health Technology Assessment (HTA) journal—the journal publishes research on the effectiveness, costs, and broader impact of healthcare technologies used on the NHS, including the results of clinical trials funded by the NIHR Health Technology Assessment Programme.
**Results**

A total of 553 articles were identified (see Fig. 1). Of these, 278 were identified on clinicaltrials.gov and 159 were registered before 2011. [L.F.] applied the inclusion criteria to a subsample of 79/159 clinicaltrials.gov articles from 2010 or earlier. In this subsample, only one trial was found to meet the inclusion criteria. It was decided to omit the 159 clinicaltrials.gov trials registered before 2011 from the review. This decision is justified by the work of Hatfield et al that found that adaptive designs were increasingly used between 2012 and 2013. Given the small number of articles identified in the subsample, it is unlikely that many trials have been missed.

Thirty-seven trials met the inclusion criteria and were subject to full data extraction.

**Trial Characteristics**

All trial characteristics are summarized in Table 2. The types of adaptive designs identified are summarized in Table 3. One trial did not provide sufficient information to assess the methods used. It was common for multiple adaptations to be implemented in a single trial. Table 3 includes all the adaptations.

The rationale for choosing an adaptive design was clear in 38% (14/37) of trials. The most common rationale was to check the uncertain assumptions made at the design stage of the trial. For example, the EVIDENCE study identified that there was a lack of information to inform their sample size. They preplanned an interim analysis to re-estimate the required number of patients to achieve sufficient statistical power.

**Health Economics in the Design**

A trial protocol was identified in 73% (27/37) of the trials. The prespecification of health economic analyses was limited with 41% (11/27) of trials not providing any detail and 59% (16/27) providing only limited detail in the trial protocol, such as a paragraph outlining that a Markov model would be used for the health economic analysis but little further elaboration. A total of 15% (4/27) of trials included a full analysis plan for their proposed statistical analyses in their protocol, and 85% (23/27) provided limited detail. Fifty-two percent (14/27) of the trials reported limited detail relating to both their health economic and statistical analyses. Some trials may have reported a full statistical analysis or health economic analysis plan in a separate document not appended to the protocol, which we have not captured.

The role of health economic outcomes in the design of the adaptive trials was limited (see Table 4). “GDHT,” “PRESSURE-2,” and “OPTIMA” were considered to have used health economics in their design. The OPTIMA trial listed a health economic outcome as a primary outcome; nevertheless, this was not considered in any sample size calculation. The Persephone study listed costs and quality of life outcomes in relation to their study design, but it was not clear what role these outcomes took.

OPTIMA considered using VOIA to inform their design and PRESSURE II planned to include an EVSI analysis at an interim.

**Health Economics in the Analysis Conducted**

Information about the analysis of the adaptive designs was extracted from trials with results available (51% [19/37]). The remaining 18 trials did not have any results at the time of data extraction and so were not included.

Of the 19 trials, we identified those thought to require adjustment to their analysis to allow for the adaptive nature of the design, specifically trials using a GSD. The reporting of the methods was not always explicitly clear and a judgment was made about the need for adjustment. Where a trial simply stated...
that there was an interim analysis (4 trials), it was assumed that this was a GSD, as this is the most common type of adaptation used in practice as identified by Hatfield et al, where 78% of phase III trials used a GSD.7,40 Two of the 19 trials were not thought to have used sequential methods or required adjustment; one used adaptive randomization and the second a sample size re-estimation.

In the remaining 17/19 trials, for which an adjustment of the point estimate for the primary and any correlated secondary outcomes was thought appropriate, there was no clear indication that the primary outcome was adjusted. In addition, none of the 17 trials indicated whether they used adjusted primary or secondary outcomes in their health economic analysis.

**Health Economic Analysis Using Interim Data**

Tessitore et al reported the interim analysis of a randomized trial on the elective repair of subclinical stenosis (ISRCTC69115386).41 The authors calculated the cost-effectiveness of the intervention using the interim data. They concluded that, given a large clinical benefit of the intervention and little difference in cost, it was unethical to continue the trial. There was no indication as to whether the treatment effect estimate was adjusted for the interim analysis.

**Health Economics in the Reporting**

Of the 19 trials with results available, 1 trial provided results only on clinicaltrials.gov and a second had information only in a short conference abstract; therefore, it was not possible to assess their

<table>
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<tr>
<td>Were any health economic outcomes a primary outcome?</td>
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<td>3</td>
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<tr>
<td>Was value of information analysis considered in the design?</td>
<td>Yes</td>
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</table>

Two trials were conference abstracts and the third did not have a protocol available.
reporting. Table 5 summarizes how well the trials reported their results.

There was little consideration for how the adaptive design might impact the clinical and a health economic analyses. One trial discussed how stopping at an interim analysis resulted in less data and therefore greater uncertainty in the health economic analysis. The authors also acknowledged that this would likely affect the generalizability of their results. It was clear for only one trial that prior interim results were available and were discussed at a conference and disseminated to trial participants.

Exemplars

The following trials highlight the use of adaptive designs and health economics as part of the clinical trial process. None of the exemplars seem to use health economics and adaptive designs to their full potential or consider the impact that using data from an adaptive design might have on their analysis. Nevertheless, given the limited research and awareness in this area, these trials illustrate the potential use of these methods.

Exemplar 1: OPTIMA Trial

The optimal personalized treatment of breast cancer using multiparameter analysis (OPTIMA) trial illustrated how VOIA methods could be used to inform the design and conduct of an adaptive design. The OPTIMA trial was designed to explore the personalized treatment of breast cancer by using laboratory tests to determine who should receive chemotherapy. This trial was an adaptive design with two interim analyses assessing futility and noninferiority.

The OPTIMA trial was preceded by a cost-utility analysis using health economic modeling to determine the cost-effectiveness of genomic test-directed chemotherapy and chemotherapy for all patients with chemotherapy directed by one of the tests under consideration, was £8,397,961 for the 10-year incident population, suggesting value in carrying out this research design. Nevertheless, this calculation does not appear to have informed the sample size calculation for the OPTIMA trial. Nevertheless, this calculation does not appear to have informed the sample size calculation for the OPTIMA trial.37

The OPTIMA program of research highlighted the opportunities to use VOIA to design efficient trials by including a stop-go decision before the full trial. A possible extension of these methods could have been to use the stop-go criteria at the interim

<table>
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<tr>
<td>Drop-the-loser</td>
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<tr>
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<tr>
<td>Futility</td>
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<tr>
<td>Futility and noninferiority</td>
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<td>2</td>
</tr>
<tr>
<td>Futility and safety</td>
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<td>2</td>
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<tr>
<td>Futility and safety and efficacy</td>
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<tr>
<td>Interim†</td>
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</tr>
<tr>
<td>NA</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

All adaptations discussed in a particular trial are included. Therefore, percentages are expressed in terms of the total number of adaptations.

†Interim denotes a trial where an interim examination of the data was mentioned but it was not possible to ascertain the motivation or methods used.
analysis to inform whether to stop or continue with the adaptive trial with appropriate adjustments.

**Exemplar 2: GDHT trial**
The GDHT study for patients with proximal femoral fracture included an interim analysis on efficacy and safety after 100 (from a planned 460) patients had been recruited. At this point it was decided to continue with the trial; nevertheless, after 50 further patients were enrolled over the following 12 months, the decision was made to stop the study.32-34

Before the trial, the authors developed a probabilistic decision analytic cost-effectiveness model. The pretrial modeling highlighted that postoperative complications heavily influence the cost-effectiveness of GDHT, and so the trial was designed to assess the risk of postoperative complications and their influence on quality of life. The pretrial model was then used for a VOIA using interim data. Although this VOIA was not preplanned, the authors highlight the potential for VOIA to be used in this way. This study is a useful case study for using VOIA during an adaptive design to inform whether it is cost-effective to continue with a trial-based health economic grounds.

**Exemplar 3: PRESSURE 2 trial**
The PRESSURE 2 trial aimed to determine the clinical effectiveness and cost-effectiveness of high specification foam and alternating pressure mattresses for the prevention of pressure ulcers.35 Because there were no results available at the time of data extraction, only the use of health economics in the design of the trial was considered. The PRESSURE 2 considered the cost-effectiveness of the research using interim data as part of an EVSI calculation. This analysis will use the interim data to determine whether it is cost-effective to continue with the trial from an NHS ‘decision makers’ perspective. This illustrates how health economic outcomes can be used as part of the interim analysis of an adaptive design.

**Discussion**
In our review of 37 clinical trials with an adaptive design and health economic analysis, only 3 trials used health economic outcomes in the design, and none of the trials seemed to appropriately adjust the health economic outcomes to account for biases introduced by the adaptive study design. One study used health economic outcomes at the interim analysis in the 19 trials with results. The reporting of health economic results was suboptimal for all trials.

**Trial Characteristics**
We found that the majority of trials were UK based and 68% (25/37) of trials were publicly funded. In the previous review by Hatfield et al, adaptive designs were found to be predominantly conducted in the United States and Canada.1 In addition, Hatfield et al1 and Stevely et al27 found that industry-funded trials were more common with 101/143 and 35/68 trials, respectively. This contrast could reflect the important role of health economic analyses in healthcare decision-making in the public UK setting.1

**Design**
Although VOIA was considered by two trials, none discussed using VOIA to inform their adaptive design, such as the optimal number of interim analyses. This highlights a missed opportunity to potentially increase the efficiency of adaptive designs by using health economic outcomes to identify the most cost-effective design.

**Analysis**
We found that many authors were not adjusting their clinical or health economic analyses to allow for the adaptive nature of the trial. A similar finding was reported by Stevely et al,27 who found that the bias correction for early stopping (for clinical effectiveness outcomes) was reported only in 7% (3/46) of GSDs.

The interim analysis of an adaptive design presents an opportunity to maximize the available interim data by considering:

- Clinical effectiveness
- Cost-effectiveness of using a cost-effectiveness analysis
- Cost-effectiveness of the research using a VOIA

Currently these opportunities are rarely being used.

**Reporting**
We identified that the reporting of adaptive designs with health economic analyses was poor. Reporting guidelines for the results of clinical trials impacts the design, conduct, and analysis by leaving no place for bad practice or poor choice of methods to be hidden.26 Poor reporting makes it difficult for researchers using the results of the trial to identify whether an adaptive design was used and that analyses may need to be adjusted. Given the importance of cost-effectiveness to decision makers, it is vital that information can be easily identified so that the whole body of evidence can be considered. There is also no opportunity for researchers to learn from past research to improve their own adaptive designs with a health economic analysis. These findings reiterate Stevely et al,27 who found that reporting of clinical outcomes was limited and highlight that this issue also extends to health economic outcomes.

**Reflection on the Current Methodological Literature**
The use of health economics to inform the design and interim monitoring of adaptive designs has received some attention in the methodological literature. A number of authors use Bayesian decision theory with dynamic programming methods to incorporate costs and utility into sequential decision problems. Berry and Ho93 determined stopping boundaries for a one-sided sequential clinical trial, where consequences of possible decisions were considered explicitly on a monetary scale. Their approach allows the trial to stop early if there is sufficient evidence to suggest that it is futile to continue. This approach has been extended by authors such as Lewis et al,44,45 Cressie and Biele,46 and Müller et al.47

More recently, Willan and Kowiger46 considered the use of EVSI methods to determine the optimal sample size for multistage clinical trials. This work was extended by Chen and Willan47 to an industry perspective. Pertile et al51 used a Bayesian sequential economic evaluation model to approximate an optimal stopping rule based on cost-effectiveness. The rule considers the cost of carrying out further research against the value gained from having a more accurate estimate of cost-effectiveness. Chick et al51 extended this to consider trials with a delay in observing the response.

This review has highlighted how these methods are yet to translate into practice. Possible explanations are that some of the proposed methods have a high computational burden,52-54 requiring backward induction methods, and can be considered only in a limited number of scenarios. Newer methods have not yet had the chance to be applied in practice and reported.48,50,51

At the time of writing, we are not aware of any literature that discusses the impact of adaptive designs on the health economic analyses.
analysis, specifically the potential for bias to be introduced by the adaptive design.

Limitations of This Work

The sample of adaptive designs reviewed were identified from a range of sources; nevertheless, this will not include every adaptive design. We chose to exclude trials identified using clinicaltrials.gov before 2011; nevertheless, given the limited use of adaptive designs before this time we do not believe that this exclusion will affect the representativeness of our sample. The level of detail provided on clinicaltrials.gov can vary, which meant that many trials were excluded because there was insufficient information to determine whether it was an adaptive design. This issue was also faced by Hatfield et al. The trials in which a health economic analysis was planned after the adaptive design was proposed were not captured. There are likely to be consequences for these types of analyses if they use data from adaptive trials too and this should be considered when planning such analyses.

A number of the main trial reports did not give details about health economic analyses conducted, and so it was difficult to ascertain the methods used and whether any adjustments were made for the adaptive nature of the trial.

Recommendations

We recommend that proposed health economic analyses should be outlined in a detailed Health Economic and Decision Modelling Analysis Plan (HEDMAP) before the start of an adaptive design. Although this is recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) this was not commonplace. Prespecification of all analyses is important in adaptive designs to protect the validity and integrity of the results, especially for trials using health economic analyses to inform interim decision making. Ideally, guidance developed for the use of health economic analysis plans should consider specific guidance for adaptive designs.

To improve the reporting of the health economic analysis of adaptive designs the CHEERS checklist should be extended for adaptive designs. The ongoing ACE project aims to develop CONSORT guidelines tailored to the specific requirements of an adaptive design, an important issue identified in reviews by Stevely et al., Mistry et al. and Bothwell et al. Extending this statement will address some of the reporting issues identified in this review; nevertheless, the CONSORT guidelines do not include the reporting of health economics. Appropriate points from these guidelines should be applied to clinical trial registries and in the trial protocol.

Conclusions

Appropriate consideration is rarely given to the health economic analysis of adaptive designs. This could mean that trials are stopping early based on efficacy outcomes but with insufficient evidence to demonstrate the cost-effectiveness of the health technology; continuing unnecessarily when there is already sufficient evidence for decision making with respect to cost-effectiveness; and drawing incorrect conclusions in the health economic analysis as the bias introduced by the study design has not been accounted for in the analysis.

Exploration of the methodological challenges and identification of the practical and ethical issues are required to establish whether adaptive designs and health economic analyses can be used together to increase the efficiency of health technology assessments without compromising accuracy.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.11.008.

REFERENCES


