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

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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-effectivenes, 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 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[6] 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]

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

Name	Description
Group Sequential Design (GSD)	Interim analyses are carried out after groups of patients have reached the outcome of interest.[9,10] 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.[11] Methods exist to adjust for this bias in the treatment effect estimate and its confidence interval as well as correlated secondary outcomes.[11-13]
Sample Size Re-estimation	The sample size calculated before the trial commenced is updated using information collected up to the interim analysis.[14] 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.[15] Generally, these methods are recommended only to increase the sample size.[15]
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.[14] This can increase the probability of success of the trial and allow new participants to receive the most promising treatment.[14]
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.[16]
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.[17]
Expected Value of Perfect Information (EVPI)	The expected value of perfect information (EVPI) considers the scenario where further research would eliminate all decision uncertainty,[18] representing the most that can be gained from further research.[19] The EVPI can take only positive values.[20] 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.[21]
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,[22] 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.[23]
Economic Evaluation	"Comparative analysis of alternative courses of action in terms of both their costs and consequences."[19]

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.[19] Value of information analysis (VOIA) methods assess whether it is worthwhile collecting further information to inform a decision.[19] Table 1 provides a summary of key terms in health economic analyses; Drummond et al[19] provide a comprehensive summary.

Objectives

Adaptive designs could compromise accuracy by introducing bias into health economic analyses. This has the potential to negatively affect patients and healthcare providers. It is important to have a clear understanding of how adaptive designs and health economics are considered together in the design, analysis, and reporting of clinical trials.

The primary aim of this review is to establish how health economic outcomes are used in adaptive trials in the design, such as secondary outcomes or informing sample size using VOIA methods; analysis, such as whether adjustments were used to account for the adaptive nature of the trial; and reporting, by applying elements of established reporting guidelines.[24,25]

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).[26]
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[7]—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[27]—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.

6. Known adaptive designs—identified by contacting experts in statistics and health economics—known to the research team and via emails sent to the online forums AllStat (Sep. 28, 2016) and HealthEconAll (Sep. 29, 2016).

To identify articles on clinicaltrials.gov and the *HTA* journal the search strategy implemented by Hatfield et al[7] (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.11.008) was used. The strategy aimed to identify trials with an adaptive design using common words such as "adaptive," "sequential," and "interim." Development and validation of the strategy is reported in Hatfield et al.[7]

Inclusion Criteria

Five reviewers [F.A., R.B., L.F., S.A.J., K.P.] identified articles that met criteria adapted from Hatfield et al[7]:

1. Trial documentation available in English
2. Phase III clinical trial
3. Trial investigating an intervention(s) on humans with a comparator
4. Registered or published before Aug. 1, 2016
5. Multiple treatment arms
6. An adaptive design clinical trial—defined to be a trial with any preplanned early examination of the data, including any monitoring of the data by a data monitoring and ethics committee (DMEC) where it is clear that there had been or there is a planned formal analysis of the data
7. A planned health economic analysis

The chief investigator for clinical trials with a preplanned adaptive design but with no clear health economic analysis was contacted via email to ask whether any health economic analyses were carried out.

Data Extraction

For trials that met the inclusion criteria, information was extracted relating to their characteristics, design, analysis, and reporting. A data extraction sheet was developed using items from five key checklists or quality assessment processes in the areas of clinical trials, health technology assessment, and cost-effectiveness, including the CONSORT statement and the CHEERS checklist.[24,25,28-30]

We identified trial documentation using the information from trial registries, protocols, and journal publications (identified via MEDLINE and Google Scholar). When a large number of results were returned by a database, they were sorted by relevance and date to identify the most relevant publications. To assess the reporting of the trial results we used the main trial paper or *HTA* monograph.

Inclusion criteria were applied and data were extracted independently by two reviewers. Any discrepancies were resolved by a group discussion. All data were checked and cleaned by [L.F.]. Some of the information extracted, such as the level of detail reported about health economics in the protocol and reporting questions, required a subjective decision, and [L.F.] therefore reviewed data extracted by the team and made a final decision for consistency. Any subsequent changes were documented.

Outline of Analysis

A descriptive analysis was undertaken to provide an overview of how health economics was used in the sample of adaptive designs. Continuous variables were summarized using their mean and standard deviation (SD). Categorical variables were summarized using counts and percentages.

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.[7] 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[31] 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,"[32-34] "PRESSURE-2,"[35] and "OPTIMA"[36-38] 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.[39]

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

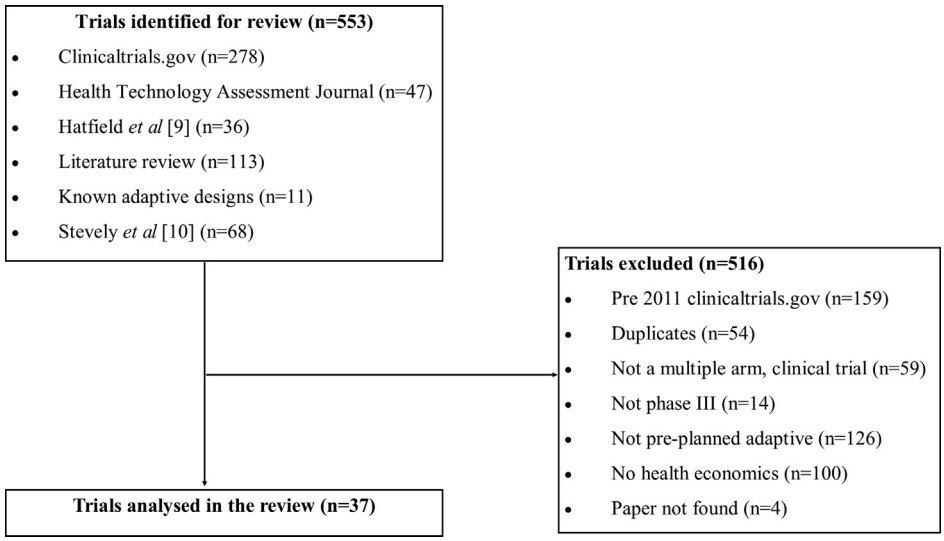

Fig. 1 – Flow of articles through the review.

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.

Table 2 – Summary of the trial characteristics meeting the inclusion criteria.

Characteristic	Category	n	%
State	Ongoing	8	22
	Recruiting	7	19
	Completed	20	54
	Not clear	2	5
Country of chief investigator	Canada and USA	9	24
	China	1	3
	Europe (not including UK)	9	24
	UK	17	46
Funder	Private	6	16
	Public	25	68
	Private and public	2	5
	Not clear	4	11
Experimental treatment	Medicinal	17	46
	Device	3	8
	Educational	2	5
	Psychological	0	0
	Complex intervention	0	0
	Other	15	41
Comparator	Active	35	95
	Placebo	2	5
Therapeutic area	Oncology	11	30
	Cardiology	5	14
	Vascular and hematology	4	11
	Spinal	2	5
	Other	15	41

Health Economic Analysis Using Interim Data

Tessitore et al reported the interim analysis of a randomized trial on the elective repair of subclinical stenosis (ISRTC69115386).[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 3 – Summary of how health economic outcomes were considered in the design of the adaptive design clinical trials in the review.

Characteristic	Category	n	%
Were health economic outcomes considered in the design?	Yes	3	8
	No	32	86
	Not clear	2	5
Were any health economic outcomes a primary outcome?	Yes	1	3
	No	34	92
	Not clear	2	5
Were health economic outcomes considered in the sample size calculation?	Yes	0	0
	No	34	92
	Not clear	3	8
Was value of information analysis considered in the design?	Yes	2	5
	No	32	86
	Not clear	3	8

Two trials were conference abstracts and the third did not have a protocol available.

Table 4 – Summary of the adaptations used in a trial.

Type of adaptation	n	%
Adaptive randomization	1	2
Drop the loser	2	3
Internal pilot	12	20
Sample size re-estimation	7	12
Efficacy	3	5
Efficacy and futility	4	7
Efficacy and safety	9	15
Futility	5	8
Futility and noninferiority	1	2
Futility and safety	1	2
Futility and safety and efficacy	5	8
Interim*	4	7
NA	1	2

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.

Table 5 – Summary of the level of reporting in the adaptive design (AD) clinical trials in the review.

Characteristic	Category	n	%
Was the trial identified as an adaptive design in the title?	Yes	1	3
	No	16	43
	NA	20	54
Was the economic evaluation or more specific identified in the title?	Yes	5	14
	No	12	32
	NA	20	54
Was the economic evaluation or more specific identified in the abstract?	Yes	8	22
	No	9	24
	NA	20	54
Were health economic outcomes discussed on the main trial paper?	Yes	9	24
	No	8	22
	NA	20	54
Discussion of how the adaptive design might have impacted on the health economic analysis	Yes	1	3
	No	14	38
	Trial stopped before first interim	2	5
	NA	20	54
Was the potential for bias in the results discussed?	Yes	0	0
	No	15	41
	Trial stopped before first interim	2	5
	NA	20	54
Was the generalizability of the findings from the adaptive design discussed?	Yes	1	3
	No	14	38
	Trial stopped before first interim	2	5
	NA	20	54
Were lessons learnt from using the adaptive design discussed?	Yes	0	0
	No	15	41
	Trial stopped before first interim	2	5
	NA	20	54
Were prior interim results provided or discussed?	Yes	1	3
	No	11	30
	Trial stopped before first interim	2	5
	Trial stopped at first interim	3	8
	NA	20	54

Questions have been adapted[9,27,29-31] (n = 37).

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.[36-38] 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[38] using health economic modeling to determine the cost-effectiveness of genomic test-directed chemotherapy and chemotherapy for all patients. VOIA was used to inform the value of conducting further research and highlight areas that required further work. This showed substantial uncertainty in the cost-effectiveness, and hence the OPTIMA prelim study was planned.

The OPTIMA prelim trial (ISRCTN42400492) was used to assess the feasibility of a larger trial. One of the main objectives was to evaluate the performance and health economics of different laboratory tests to determine what would be evaluated in the main trial. The analysis highlighted considerable uncertainty in the cost-effectiveness of all the tests.[42] A VOIA suggested that there was high value in conducting further research. The EVSI calculation for a large trial with 2500 patients per arm, comparing 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.[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

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.[7] In addition, Hatfield et al[7] and Stevely et al[27] 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 the intervention 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.[24] 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 Ho[43] 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 Kowiger[48] considered the use of EVSI methods to determine the optimal sample size for multistage clinical trials. This work was extended by Chen and Willan[49] to an industry perspective. Pertile et al[50] 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 al[51] 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

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.[7] 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)[55] this was not commonplace. Prespecification of all analyses is important in adaptive designs to protect the validity and integrity of the results,[5] especially for trials using health economic analyses to inform interim decision making. Ideally, guidance developed for the use of health economic analysis plans[56] 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,[57] an important issue identified in reviews by Stevely et al,[27] Mistry et al,[40] and Bothwell et al.[8] 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.

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