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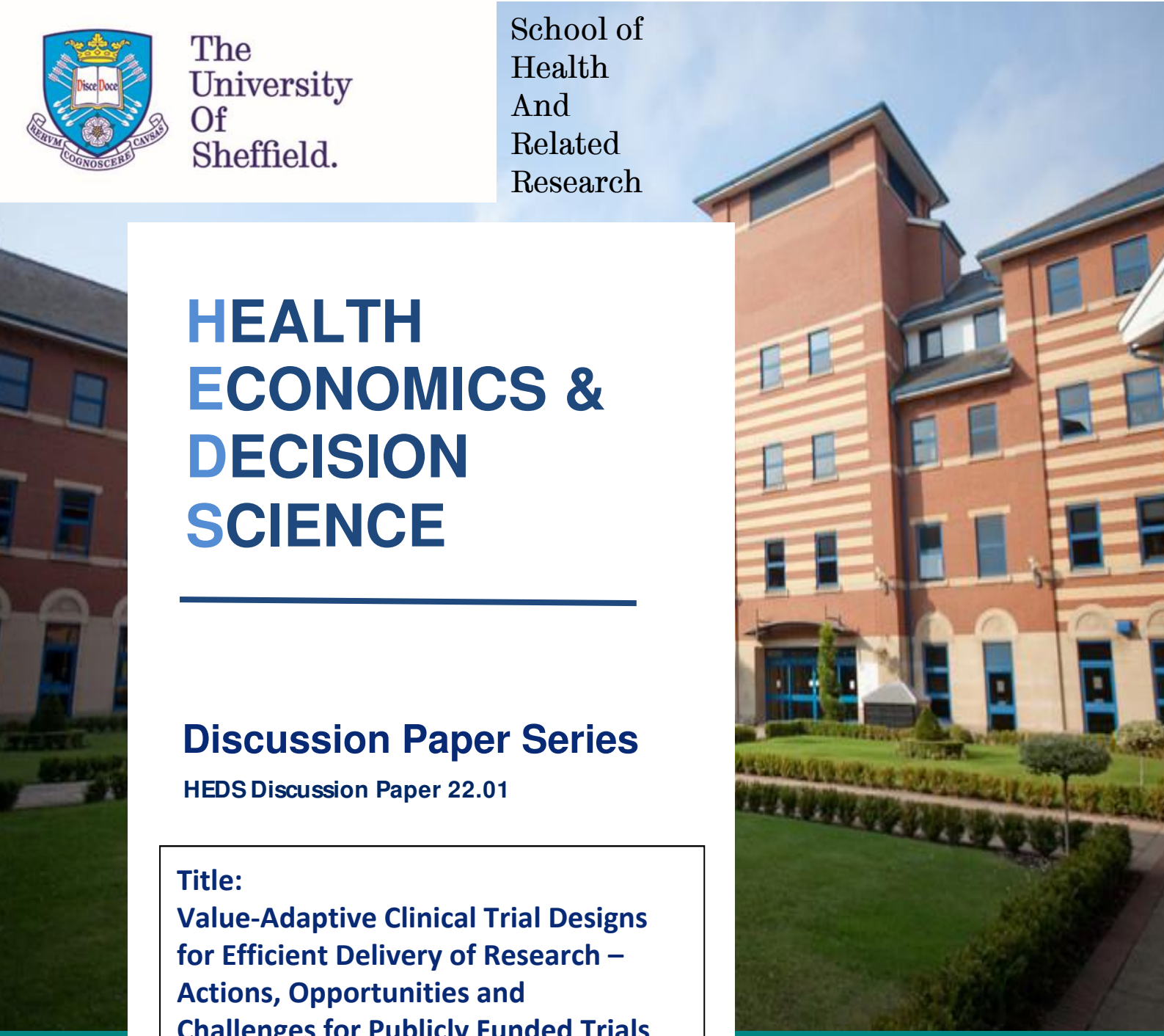

HEALTH ECONOMICS & DECISION SCIENCE

Discussion Paper Series

HEDS Discussion Paper 22.01

Title:
Value-Adaptive Clinical Trial Designs for Efficient Delivery of Research – Actions, Opportunities and Challenges for Publicly Funded Trials

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Value-Adaptive Clinical Trial Designs for Efficient Delivery of Research – Actions, Opportunities and Challenges for Publicly Funded Trials

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Abstract

Value-adaptive designs are a set of emerging methods for efficient clinical trial design that aim to maximise expected population health for the money being spent. They involve adaptive data collection processes that consider the costs of research, the expected value of information from data collection, and the health technology assessment decisions around cost-effectiveness. This topic is important to clinicians practising in publicly funded healthcare systems as they rely on evidence-based treatment strategies that have been shown to be effective in comparison to alternative interventions. Therefore, more efficient, and accurate research studies potentially offered by value-adaptive designs can feed into real decisions and implementation in the care provided by the National Health Service (NHS). Doing so offers the potential to save research costs, to bring the better technology to patients sooner, and to reduce the number of patients randomised into the trial. In this article, we review these emerging methodologies, summarise recent methodological advances, and assess the opportunities they offer for improving the efficiency of publicly funded trials. We also discuss the steps that might be taken by funders, clinicians, trial teams, the public and healthcare decision makers to successfully deploy these methods.

Keywords: Adaptive clinical trial; Cost-effective research; Health economics

1 Introduction

1.1 Why this topic is important

There is increasing interest in the use of adaptive designs to improve the efficiency of clinical trials [1,2]. Adaptive clinical trials can prevent participants from being needlessly randomised and save the limited resources available for conducting publicly funded research [3]. Little work has been done to assess how much value these designs may deliver for health services and their patients. Value-adaptive designs are a set of emerging methods for efficient clinical trial design. The value-adaptive approach is motivated by two key ideas: monitoring accumulating trial data and using this to modify the trial (adaptive clinical trials) and allocating resources to obtain the biggest health gains for the healthcare system (value-based decision making). They involve adaptive data collection processes that consider the costs of research, the expected value of information from data collection, and the health technology assessment decisions around cost-effectiveness [4–8].

This topic is important to clinicians practising in publicly funded healthcare systems, as they rely on evidence-based treatment strategies that have been shown to be clinically and cost-effective in comparison to alternative interventions. National Health Service (NHS) service providers are directly involved in the design and running of publicly funded research alongside fulfilling their clinical responsibilities. More efficient and accurate research studies potentially offered by value-adaptive designs can feed into real decisions and implementation in the care provided by the NHS, offering the potential to save research costs, to bring the better technology to patients sooner, and to reduce the number of patients randomised into the trial. The emerging methods discussed in this paper also consider what organisations such as the National Institute for Health and Care Excellence (NICE) would call “value”. This is a combination of the clinical benefits of an intervention and the related costs to the healthcare system, allowing for accurate and well-informed decisions about which treatments are made available to patient on the NHS. Thus, the value-adaptive approach is one way to address some important concerns of patients, clinicians, research funders, and care delivery organisations.

1.2 What this paper covers

This paper builds on a project which explored the suitability of value-adaptive clinical trial designs for efficient delivery of research in the UK non-commercial sector - EcoNomics of Adaptive Clinical Trials [9]. The work was funded as part of the UK National Institute for Health Research (NIHR) Clinical Trials Unit Support Funding scheme in response to their call to support efficient/innovative delivery of NIHR research. The ENACT project team undertook a series of workshops with key stakeholders,

researchers, and collaborators from across the NIHR on the potential use and implementation of value-adaptive methods in NIHR research. In this paper we:

1. Discuss the background to existing methods of running adaptive trials, together with the assessment of clinical and cost-effectiveness within them, the meaning of "value" and value of information methods, and how the UK NIHR works to improve the efficiency of clinical trials.
2. Describe one value-adaptive approach, namely the value-based sequential two-arm design with adaptive stopping proposed in [4], and summarise the results of three retrospective case studies that apply it.
3. Highlight the potential benefits and opportunities that value-adaptive designs offer for the delivery of efficient research and action steps to implement value-adaptive designs, by stakeholder and stage of research.

1.3 Background

An adaptive design analyses accumulating trial data, at pre-specified time points, to inform changes to the trial. For example, it might stop the trial earlier than originally planned because the evidence is sufficiently convincing to suggest that the treatment does not work, or is clearly shown to be effective, or it may continue data collection because it needs a larger sample to obtain a more precise estimate of whether the new treatment is better than current care. Adaptive designs aim to improve the efficiency of clinical trials by saving financial resources, preventing participants from being needlessly randomised and bringing the better treatments to patients as soon as possible. These designs are becoming more common, and we refer the interested reader to key recent papers [1–3,10] and guidance documents [11,12]. However, despite the growing interest in these designs, little work has been done to assess how much value they may deliver for health services and their patients.

What is meant by "value" in this context? Healthcare systems have limited resources for funding both treatments and research to evaluate their effectiveness. Clinical trials play an important role in the health technology assessment process, providing evidence of both clinical effectiveness ('does the treatment work?') and cost-effectiveness ('is it good value for money?'). When NICE assesses new health technologies, it typically estimates the additional quality adjusted life years (QALYs) gained for a patient receiving the new technology compared to existing care, together with the incremental cost that is likely to be incurred by the NHS and social services in providing that technology [13]. It decides whether a new technology would be considered cost-effective and if it should be recommended for implementation in the NHS. Typically, a new treatment is considered cost-effective if it is expected to deliver one additional QALY at a cost that is less than around £20,000 to £30,000 [13]. The value of a

technology is therefore assessed by measuring, in monetary terms, the health gains it offers, in comparison to an existing technology, and comparing this with its cost relative to that technology.

The same concept of "value" has been considered in the prioritisation of research budgets and research design using value of information (VoI) methods. VoI methods are now well studied and there is substantial guidance on their use in non-adaptive designs [14,15]. The use of VoI methods has been increasing in health technology assessments in the UK [16] and the NIHR has recently required pre-trial cost-effectiveness modelling in some of its research studies including DAFNEPLUS [17,18]. The VoI approach aims to align the amount of evidence collected in a trial with the health and financial impact of health technology assessment decisions (for example, made by NICE) that are influenced by that evidence. The approach considers the improved precision of effect estimates if more data are collected, the connection between that improved precision and the assessment of cost-effectiveness of the technology versus existing comparators and the actual costs of the data collection itself. Ultimately, the purpose is to balance the costs and benefits of collecting data on participants in trials and by clinical research teams for consideration of effectiveness and cost-effectiveness.

To date there has been little connection made between VoI methods and the potential efficiencies offered by adaptive trials. Flight et al. [19] found that cost-effectiveness criteria are not routinely incorporated into the design of trials with an adaptive design. The emerging methods we discuss in this paper focus on the interlinkage between VoI assessment to inform the design of trials and the use of adaptive trial designs. Hence the term used here: *value-adaptive designs*.

We consider value-adaptive designs in the context of the NIHR. The NIHR is the main public funder of health and social research in the UK. Evidence from NIHR funded studies is used to inform national clinical guidelines and health technology assessment decisions in the NHS for new and existing health technologies. Improving efficiency of clinical trials research has been flagged as a priority by the NIHR [20], which states that it is "*keen to see the design, development, and delivery of more efficient, faster, innovative studies to provide robust evidence to inform clinical practice and policy*" [21]. The NIHR supports the delivery of novel, complex and innovative clinical trials, including adaptive trials (e.g., STAMPEDE [22], Randomised Evaluation of COVID-19 Therapy RECOVERY [23]). The methodological innovations from the NIHR are often adopted by the Association of Medical Research Charities (AMRC) and UK Research and Innovation (UKRI), which play an important part in the UK non-commercial research sector. Similar public-funders exist in other countries with developed healthcare systems, including Canada and Australia, making the findings relevant internationally [24,25].

2 The methods of the value-adaptive approach

2.1 What is a value-adaptive clinical trial?

A value-adaptive clinical trial uses cost-effectiveness criteria to adjust the design of the trial as it progresses, considering the cost of both the research and the health technologies. This is achieved by balancing the costs and benefits of continuing the trial in its current form with the costs and benefits of altering the way it operates. The value-based approach to running an adaptive clinical trial combines tools that are already used to assess the cost-effectiveness of new health technologies in the NHS for running non-adaptive trials, which we refer to as *fixed sample size designs* [26–30]. We first discuss health value and its relation to clinical trials, then value-adaptive trials.

2.2 Measuring the value of a health technology

We can measure the value of a health technology by first converting its health benefits, here we use the QALY, into a monetary measure [31]. This is achieved by multiplying the number of QALYs a technology is expected to generate for a patient by the maximum amount a decision maker, such as NICE, is willing to pay for an additional QALY- the so-called 'willingness to pay' (WTP) threshold. The technology's total cost is then obtained by measuring and summing up the costs of delivering that treatment to the individual (these costs include the cost of the drug or the intervention, the costs of administration, staff time and other resources).

These costs and benefits are then used to calculate the net monetary benefit (NMB) of a technology. This value is equal to the monetary value of the technology's benefit minus its cost:

$$NMB = WTP \times QALY - Cost.$$

Typically, we compare two technologies, such as a new drug A and a drug that is already in use (drug B). We calculate an estimate of the expected incremental net monetary benefit per patient affected by the technology adoption decision ($EINMB_{per\ patient}$), by taking the difference between (a) the expected NMB per patient on the new drug A and (b) the expected NMB per patient on the drug B already in use. If $EINMB_{per\ patient}$ exceeds zero, drug A has greater NMB than drug B, on average, and the new intervention is considered to be cost-effective. We use the cost and benefit data collected during a trial to estimate the $EINMB_{per\ patient}$, as described in Box 1.

Box 1: Summary of how to estimate the expected incremental net monetary benefit using data from a two-arm clinical trial comparing drug A and drug B

An illustration of an estimator ($\widehat{EINMB}_{per\ patient}$) of the expected incremental net monetary benefit per patient ($EINMB_{per\ patient}$) expected to benefit from drug A versus drug B is shown in Equation 1. We assume we have a trial dataset with n_A trial participants who received the new drug A and n_B participants who received drug B. An estimator of the QALYs and Costs for each treatment comes from a combination of the previously available evidence and trial data. We use these data to estimate the QALYs and the Costs for patients expected to benefit from the technology after a technology adoption decision. As the sample size increases, we become more certain of the expected net monetary benefit of each treatment and more certain as to which of the two would be considered cost-effective by NICE and should be adopted for use in the NHS.

$$\widehat{EINMB}_{per\ patient} = \left[\frac{\sum_{i=1}^{n_a} WTP \times qalyA_i}{n_a} - \frac{\sum_{i=1}^{n_a} costA_i}{n_a}\right] - \left[\frac{\sum_{j=1}^{n_b} WTP \times qalyB_j}{n_b} - \frac{\sum_{j=1}^{n_b} costB_j}{n_b}\right] \quad \textbf{(1)}$$

where $qalyA_i$ is the QALYs for participant i receiving drug A in that arm of the trial, and $costA_i$ is that same participant's NHS and social care costs.

For a population of P patients who will be impacted by the technology adoption decision, the population expected incremental net monetary benefit is $\widehat{EINMB}_{pop} = P \times \widehat{EINMB}_{per\ patient}$.

2.3 Value-based approach: measuring the value of a clinical trial

There has been growing interest in measuring the value of the research process itself [4,14–16,19]. The central idea is that a health technology assessment decision is made under uncertainty: there is always a risk that better outcomes for patients, on average, could have been achieved if an alternative decision had been made [14]. As a result, it may be valuable to collect more information – via a clinical trial, for example – to reduce the amount of uncertainty surrounding the decision, taking account of the fact that acquiring additional information – running a trial – incurs costs.

Rooted in Bayesian decision theory, VoI analysis provides a framework for comparing the value of obtaining more information with the costs of doing so. Box 2 shows four levels at which VoI analysis can be conducted [14,32]. Readers are referred to Spielgelhalter et al. [33] for an explanation of key Bayesian terminology including of prior and posterior distributions. Here we consider a value-based trial to be a design that incorporates VoI methods to maximise the value of the trial.

An advantage of the value-based approach is that it incorporates parameters that are all meaningful from a clinical, medical, or health policy standpoint and make explicit the drivers of a value-based design. They are not based on traditional type I and type II error criteria that may not adequately represent quantities such as disease prevalence, average health benefit, and incremental costs (all of which are considered by NICE).

Box 2: Expected value of information analysis for a clinical trial with a fixed sample size: terminology and concepts

Applied to the field of health technology assessment, the value of information compares the expected value of a decision made without collecting new information with the expected value after collecting new information. We can define four ideas:

1. Expected value of perfect information (EVPI): the value of acquiring perfect information about all aspects of the technology adoption decision (thereby eliminating all uncertainty),
2. Expected value of partial perfect information (EVPPI): the value of acquiring perfect information about a subset of parameters in the decision,
3. Expected value of sample information (EVSI): the value of a research design that reduces some (but not all) of the decision uncertainty by collecting information in the sample (for example, using a clinical trial),
4. Expected net benefit of sampling (ENBS) - the expected value of sample information minus the costs of acquiring the information (such as the cost of the clinical trial).

Source: Raiffa and Schlaifer [32] and Fenwick et al [14]. See also [28,29,34].

2.4 Combining the adaptive and value-based approaches

The value-adaptive approach extends the value-based approach by allowing trial decisions to depend on estimates of these costs and benefits as the data in the trial accrues. In a value-adaptive design, participants are allocated to trial arms sequentially using the accumulating data on incremental net monetary benefit to determine how long the trial should run [4,7,35,36] and how patients are allocated to each arm [8,37]. Simulations of trials can be run with value-adaptive designs to produce estimates of frequentist power, bias, and other characteristics, in line with the guidelines for reporting the characteristics of complex innovative trials [38].

2.5 The value-based sequential design

A value-based sequential design is one specific type of value-adaptive design. In a two-arm value-based sequential design, participants can be allocated in pairs and stop/go decisions are informed by the accumulating estimate of cost effectiveness, the number of outcomes observed and the cost of allocating another pair of patients to the two arms of the trial. Follow-up of cost-effectiveness data takes place after a defined period following randomisation. Section 2.6 discusses a value-based design for a sequential two-arm trial that uses trial data as it accumulates to determine an optimal stopping time. Section 2.7 discusses other value-adaptive designs.

2.6 The value-based sequential two-arm design with adaptive stopping

In this paper we focus on a value-based sequential approach that uses Bayesian optimisation techniques and dynamic programming methods to define a 'stopping rule' for a two-arm trial

[7,35,36]. The stopping rule halts the trial when the expected benefits of randomising a further pair of participants into the trial are deemed not worth the expected costs. This design will be referred to simply as the "value-based sequential design" hence forth.

A research team contemplating the use of the value-based sequential design might consider the following three steps:

1. Synthesizing prior information (past trials, related data, expert opinion, etc.) to determine the optimal value-based trial design.
2. Comparing the characteristics of possible trial designs.
3. Conducting the trial with the chosen design.

We discuss each of these steps in turn using results from three-case studies, described in Box 3, to illustrate the approach.

Box 3: Description of three trials used for a case study analysis demonstrating how the value-based sequential design can be applied in practice

ProFHER

The ProFHER trial was a pragmatic trial funded by the NIHR to compare surgical and nonsurgical intervention (sling immobilisation) for the treatment of proximal humerus fracture [39]. It was designed using a traditional, frequentist, approach which randomised 250 participants to the two arms of the trial, over the course of two and a half years. The trial cost £1.5m and concluded that surgery was neither more effective than sling, nor more cost-effective, at two years' follow-up. A follow-up at five years found that these results were unchanged [40].

Big CACTUS

The Big CACTUS trial evaluated the clinical and cost-effectiveness of a computer-based speech and language therapy (CSLT) in patients with aphasia following stroke. The trial was funded by the NIHR Health Technology Assessment programme (HTA - 12/21/01) with a budget of £1.4m to cover research costs. The trial used a traditional, frequentist approach that randomised 278 participants to three treatment arms. The long-term cost-effectiveness of the CSLT was assessed using a model based cost-utility analysis [41]. The trial showed that CSLT led to significant improvements in word-finding ability but these did not generalise to conversation or patients' perceptions of communication, participation, and quality of life [42]. The cost-effectiveness analysis suggested that CSLT is unlikely to be considered cost-effective in the whole population investigated but may be more cost-effective for people with mild to moderate word-finding abilities.

HERO

The HERO trial was a double-blind, randomised, clinical trial that evaluated whether hydroxychloroquine is superior to placebo for the treatment of hand osteoarthritis (OA). Follow-up took place at six months for the clinical evaluation and at 12 months for the economic evaluation. The study was funded by Arthritis Research UK (now Versus Arthritis UK) and had a budget of £900,000 [43,44]. The trial showed that hydroxychloroquine was no more effective than placebo for pain relief in patients with moderate to severe hand pain and radiographic osteoarthritis. Nor was hydroxychloroquine found to be cost-effective [45].

2.6.1 Synthesizing prior information to determine the optimal value-based trial design

A first step is to synthesize prior information (e.g., past trials, related data, expert opinion, etc.) to assess the values of parameters that determine the best value-based trial design. In general, the following information is required to implement a value-based sequential design:

1. Willingness to pay threshold (discussed above);
2. Fixed and variable costs of carrying out the research;
3. Size of the population which will benefit from the health technology assessment decision;
4. Sampling variance of the incremental net monetary benefit in the population of participants considered;
5. Delay between randomisation and observing the measure of incremental net monetary benefit for each participant;
6. Maximum number of participants which may be recruited to the trial;
7. Rate of recruitment in the trial.

Techniques to inform the prior distribution for the unknown expected incremental net monetary benefit of the new versus existing technology include subjective probability elicitation [46] and empirical Bayes methods using pilot data [47].

The optimal value-based sequential design provides a stopping boundary for the trial that maximises the overall value delivered for the funder, measured by the net monetary benefit that patients expect to receive from the health technology assessment decision, less the cost of the research. Figure 1 illustrates the resulting stopping boundary. It shows that there are three distinct stages to the trial.

1. Stage I – participants are randomised to the two treatments, but data are not available until the defined follow-up period is reached. For example, costs and QALYs may be observed for each individual 12 months after they are randomised. Thus, when the first participant's data are analysed, several participants (depending on the delay in observing data and the trial recruitment rate) have been randomised and are awaiting outcome data 'in the pipeline'.

2. Stage II - data start to be observed and there is the option to randomise further participants or stop recruitment into the trial. The boundary demarcates the region where the trial should continue to recruit participants (the continuation region - shaded purple). The shape of the stopping boundary will depend upon the size of the population to benefit, the variable costs of research, the sampling variance of incremental net monetary benefit of participants in the trial, and the average number of pipeline participants.

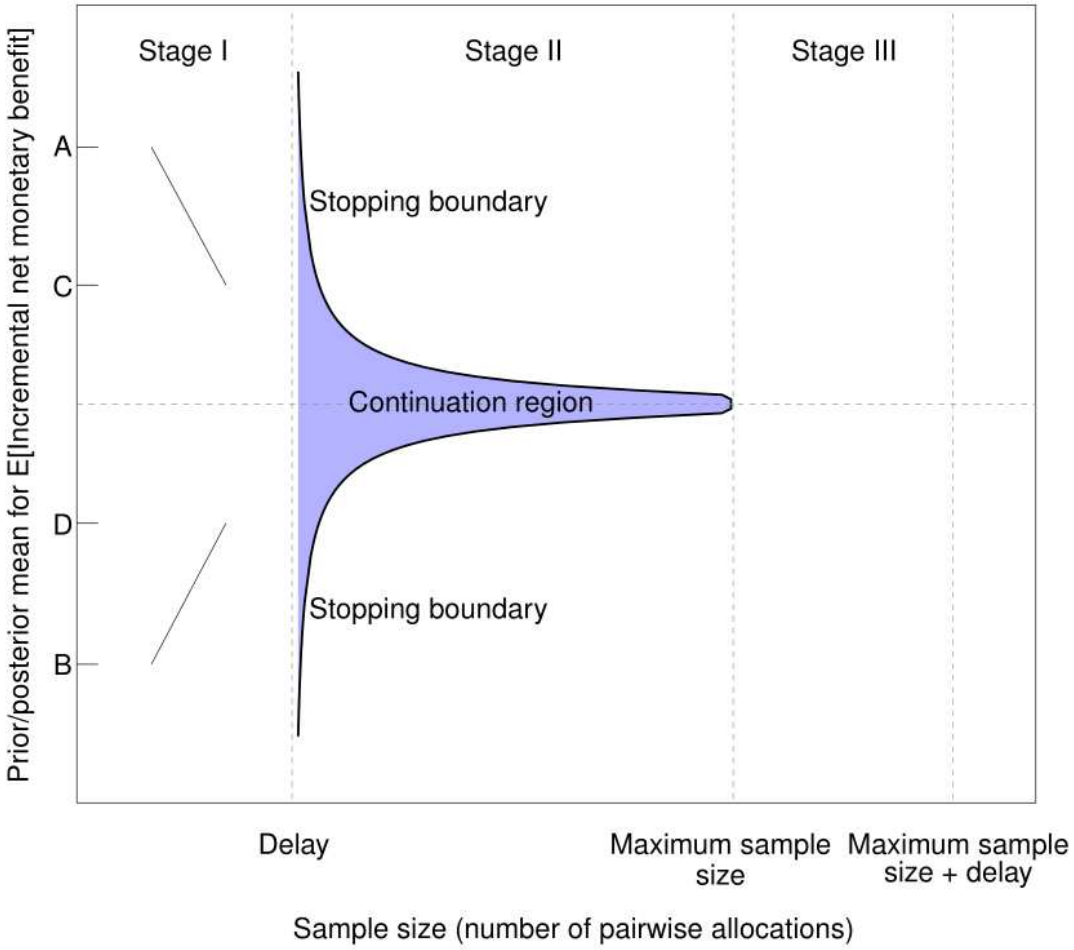
3. Stage III - recruitment is finished (the boundary has been crossed or the maximum planned sample size has been reached) and data from participants continues to be observed as they reach the follow-up time point. The technology which is favoured as best based on all data (not just observations to the time when the sampling ceases) is selected for adoption.

In Figure 1, the vertical axis displays the prior/posterior mean of the expected incremental net monetary benefit based on data collected so far. Based on prior information, before the trial begins, it is possible to determine whether it is best to run no trial at all, run a fixed sample size design or to use the value-based sequential approach. If the prior mean is sufficiently high (above A), the expected value of immediately adopting the new technology would exceed the expected value of running any trial to assess which technology is best. This might happen, for example, if earlier-stage trial data were extremely positive so that an immediate treatment adoption was warranted.

If the prior mean is sufficiently low (below point B), the existing evidence before the trial suggests that the new technology is expected to be considerably less cost-effective than current technology. In that case, the expected reward of any value-based trial would not exceed the reward of immediately adopting (continuing to use) the standard technology.

For values of the prior mean between the points labelled C and D, it is optimal to run a value-based sequential design. For values of the prior mean between the points labelled A and C, and between the points B and D, the optimal value trial design is a fixed sample size. The sample size of the fixed design is determined by analysing the EVSI minus the cost of conducting the trial [48], and is calculated to be the values in Figure 1 under Stage 1, for the ranges between A and C and then B to D.

Figure 1: Illustration of the optimal stopping boundary for a value-based sequential two-arm design with adaptive stopping.



2.6.2 Comparing the characteristics of possible trial designs

Once candidate trial designs have been identified we can compare their characteristics to help determine the most appropriate design for a trial. Performance characteristics explored by Forster et al [49] include the expected sample size of the trial, its expected cost, the overall expected value delivered to the healthcare system by the trial and the probability that the trial concluded that one of the two treatments was cost-effective.

To estimate these characteristics before the trial begins, a trial team can use the software provided by Chick et al [50] and pre-trial simulations. The actual data accrued during a trial represent just one realisation of how the trial data emerge. Pre-trial simulations can be used to model how the data might arrive in a different order many times. As the three case studies listed in Box 3 were retrospective, we used a non-parametric bootstrapping analysis to simulate possible trial results, as

the original trial data were available. In practice, alternative approaches might be used such as parametric bootstrap approaches [51].

Table 1 summarises some of the operating characteristics from the analysis of these three trials, based on Monte Carlo simulations (5000 bootstrapped samples for each simulated trial). The table allows us to compare the potential performance of the designs and can be used to inform stakeholder discussions about the most appropriate design for a trial. In this analysis we compared

(i) the original, frequentist fixed sample size design,
(ii) a value-based one-stage design that maximises the ENBS (described in Box 2),
(iii) a value-based sequential two-arm design with adaptive stopping with a maximum sample size equal that of that value-based one-stage design.

The operating characteristics of the three designs are case-study specific and should be compared carefully, considering both their qualitative and quantitative nature, as well as the perspective of the body responsible for commissioning the research and its jurisdiction. See Forster et al [49] for details.

In all three case studies, the expected net benefit delivered to the health care system by the value-based sequential design (iii) is higher than the expected net benefit delivered by the value-based one-stage design, by approximately one order of magnitude (ii) and the trial itself. This is expected: when the value-based sequential design has a maximum sample size that is equal to the optimal sample size of the value-based one-stage design, the sequential nature of the design means the trial can be stopped when the expected benefits of randomising a further pair of patients to the two arms of the trial is not worth the cost (an option that is not available in the value-based one-stage design). The largest gain in expected net benefit of the value-based sequential model over the value-based one-stage model was found in the CACTUS case study (approximately 7%). The results from the ProFHER and HERO case studies show the gain to be smaller (less than 1%).

In the CACTUS case study, the optimal sample size of the value-based one-stage design (ii) is 39% higher than the sample size of the original Big CACTUS trial (i), so that the trial cost of the value-based one-stage design (ii) is 14% higher. But the value-based sequential design (iii) has an expected sample size which is roughly equal to the original Big CACTUS trial (it is only 5.3% larger), whilst delivering additional expected net benefit (+11% when compared with the original design of the trial). In contrast, for the HERO case study, the optimal sample sizes of the value-based one-stage design (ii) and value-based sequential design (iii) are 40-43% higher but deliver little additional expected net monetary benefit (less than 1%).

	ProFHER case study % increase over original trial (i)	CACTUS case study % increase over original trial (i)	HERO case study % increase over original trial (i)
Expected sample size (maximum sample size)			
(i) Original trial	125	95	124
(ii) Value-based one-stage	112 (-10%)	132 (+39%)	177 (+43%)
(iii) Value-based sequential	73 (-42%)	100 (+5.3%)	174 (+40%)
Expected cost associated with conducting the proposed trial design (£000,000)			
(i) Original trial	£1.47m	£1.22m	£0.84m
(ii) Value-based one-stage	£1.42m (-3.4%)	£1.39m (+14%)	£0.92m (+11%)
(iii) Value-based sequential	£1.25m (-15%)	£1.24m (+1.6%)	£0.92m (+10%)
Expected net monetary benefit (£000,000)			
(i) Original trial	£51.2m	£3.54m	£52.0m
(ii) Value-based one-stage	£51.2m (+0.01%)	£3.60m (+1.7%)	£52.0m (+0.01%)
(iii) Value-based sequential	£51.2m (+0.27%)	£3.85m (+8.8%)	£52.1m (+0.19%)
Estimated probability of concluding the new technology is cost-effective			
(i) Original trial	0.20	0.32	0.39
(ii) Value-based one-stage	0.05 (-75%)	0.27 (-16%)	0.44 (+13%)
(iii) Value-based sequential	0.09 (-55%)	0.34 (+6.3%)	0.44 (+12%)

Table 1: Summary of the average trial results (5000 simulated trials) in three case-studies comparing the original frequentist fixed sample size design (i), the value-based one-stage design (ii) and the value-based sequential two-arm design with adaptive stopping with maximum sample size equal to the value-based one-stage design (iii).

The analysis for Table 1 compared the original trial, the value-based one-stage trial, and the value-based sequential two-arm design with adaptive stopping, for three case studies from the UK NHS setting (ProFHER, CACTUS, and HERO trials), under the assumption that the basic cost structure for each trial was the same. In practice, the costs might differ. For example, extra data collection and analysis costs might be incurred for continuous monitoring of data. Those costs should also be considered when choosing an appropriate design, and the framework above permits such costs to be incorporated. We note that digital technology developments are reducing those costs through time. In addition, it may be useful to allow a sequential trial to run longer than the optimal one-stage trial, if additional data would have value that would merit additional learning (such as when the value of both arms is very similar).

2.6.3 Conducting the trial with the chosen design

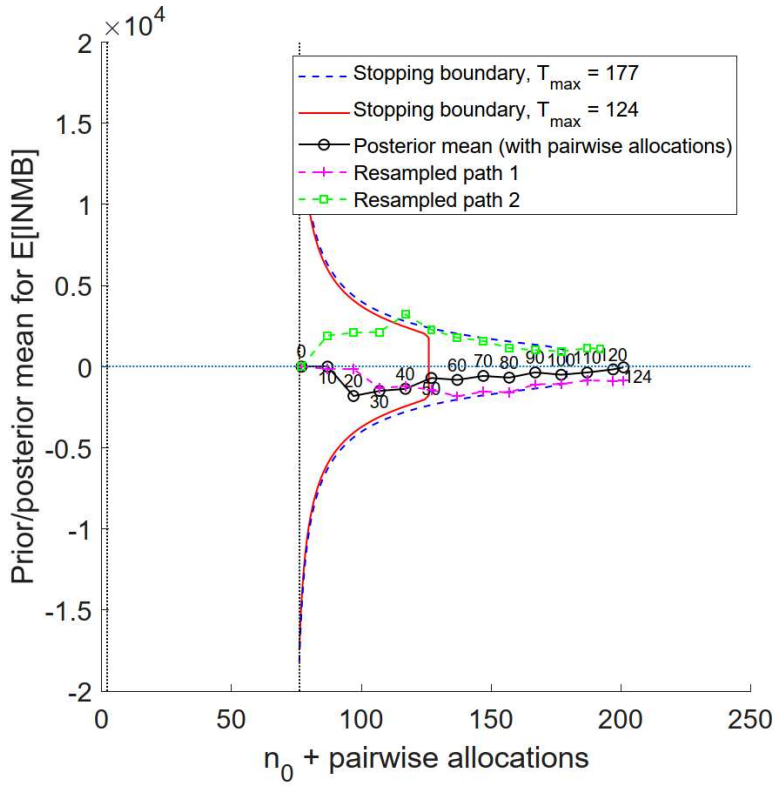
Once the trial design has been decided based on the considerations in the preceding section, the trial can be conducted. If the value-adaptive trial is selected, accruing data can be used to determine whether the trial can stop early on cost-effectiveness grounds. In each of the case studies, the actual accrued data from the trial was used to illustrate retrospectively what might have happened had a value-based sequential design been used.

Figure 2 shows the stopping boundary for design (iii) of the HERO trial - the value-based sequential design with a maximum sample size equal to the optimal sample size of the value-based one-stage design (the dashed stopping boundary with Tmax = 177). In addition, the solid red line shows the optimal stopping boundary if the maximum number of participants were constrained to match the sample size of the original trial (Tmax = 124). The actual sample path for the posterior expected incremental net monetary benefit of the HERO trial is also plotted as the solid black line with circles. In this application, the delay between treating a patient and observing data was the time to enrol 74 patients – this is reflected as the difference between the two vertical dotted lines. The figure also shows two bootstrapped sample paths – one bootstrapped trial stops earlier than the other, which would have resulted in a smaller number of patients randomised if that data had been observed in practice.

In general, a value-based sequential design would continue enrolling participants until the stopping boundary was crossed. In the CACTUS and HERO case studies, based on the stopping boundary for the value-based sequential design with a maximum of 132 and 177 participants, the trials would not have stopped early but instead incurred an increase in costs of 14% and 10%, respectively. However, continuing these trials would provide more information to increase the precision of the ultimate

technology adoption decision. For the ProFHER trial, a smaller number of observations were required, on average, because enough evidence was collected to justify a technology adoption decision relative to the cost of collecting additional observations.

Figure 2 Stopping boundary for the value-based sequential two-arm design with adaptive stopping with a maximum sample size equal to the optimal sample size of the value-based one-stage design and the observed sample path from the original HERO trial. Note that the original sample size has a smaller sample size than the value-based sequential design and so only these points are shown on the graph.



2.7 Further methods development questions for value-adaptive designs

We have introduced the value-based sequential design for two-arm trials. However, there is a range of questions that a value-adaptive framework can help to inform. In Table 2, we highlight some of those questions and discuss some ways that using a model of both trial costs and health economic benefits from health technology assessment decisions might inform the answers to those questions. In some cases, preliminary evidence is available, in the form of simulations of retrospectively analysed trials, or of results from related problems in sequential Bayesian optimisation. In other cases, there are initial results that need to be adapted and that present interesting opportunities for further work to improve the value from trials in informing health technology assessment decisions.

Opportunities exist to extend the value-based approach to help trial teams determine the optimal recruitment rate of their trial. This has been highlighted by Alban et al. [5], who discuss this based on data from the ProFHER trial (see Box 3). These methods may be used to complement research to tackle known issues with recruitment and retention in clinical trials [52].

Value-adaptive methods can be extended to the multi-arm setting, considering the adaptive allocation of participants to each arm [6,8], as well as informing the stopping time for the trial, using work from value-based and related expected VoI maximisation techniques from other fields [53–56]. An important source of potential efficiency gain for multi-arm trials is a focus on selecting the best alternative treatment with a high degree of evidence, rather than estimating the performance of each arm, including those which appear to be clearly inferior. When considering the benefits of a technology, as well as the benefits to trial participants, it is possible to incorporate the benefits to those not taking part in the trial and the population expected to benefit once the technology is made available [33]. Some of the techniques for allocating participants using an expected VoI approach in other fields do not account for the randomisation that is expected for clinical trials. Examples of adapting those tools to account for randomisation include Chick et al and Villar et al [8,57]. There are still interesting methodological developments to pursue, including the incorporation of longitudinal data, or surrogate endpoints that are correlated with endpoints.

A health technology assessment process may result in the NHS (or another decision-making body) adopting a new technology. The adoption of a new technology can incur implementation costs, such as those associated with changes to infrastructure, capacity development or redeployment, training of staff to use the new technology, etc. While these costs are not typically assessed as part of the trial design process (and were not explicitly considered in our case studies), we note that the value-adaptive design can account for such features as part of the modelling process [e.g., 3], and there is literature on the expected value of implementation which utilises similar value-based methods to the expected VoI approaches (see for example Hoomans et al and Grimm et al [58,59]).

Table 2: Additional questions of relevance to trial teams or funders that might be informed by a value-adaptive approach or by sequential learning research from other fields. INMB; incremental net monetary benefit

Type of question	Discussion
Can the value-based approach be useful to inform the optimal rate of recruitment?	A value-based trial optimises the expected population INMB minus expected trial costs. If the recruitment rate is nonlinear (e.g., a trial manager may prioritise sites for opening because they are more likely to have a higher rate of successfully enrolled and retained participants), this information can be used to optimise the recruitment rate. Alban et al [5] discuss this based on data from the ProFHER trial.
Can the fraction of participants allocated to each arm be adapted?	Ahuja and Birge [37] use dynamic programming in a group sequential trial for Bernoulli (0-1) outcomes to adaptively vary the fraction assigned to each arm during each stage based on accumulating data. This aims to improve outcomes for participants in the trial as well as the probability of correctly selecting the best treatment and can be adapted to the valued-based setting by weighting outcomes by estimates of net monetary benefit.
Can multi-arm trials be value-adaptive, to assess several arms, or several combinations of therapies, or for Phase II/III dose finding?	Multi-arm trials may have correlated mean INMB for different arms. For example, in a dose-finding trial, similar dose levels may have a more similar mean INMB than very different dose levels. Adaptive allocation policies for highly sequential value-based multi-arm trials have been proposed and show promise in identifying optimal doses (as compared to precisely estimating the entire dose-response curve, even less-effective doses) [6,8].
Can the health outcomes of participants in the trial be accounted for when valuing population health, in addition to their value in informing cost-effectiveness estimates?	The case study examples assume participant benefits once a treatment is adopted in practice are to be optimised. The benefits for participants in the trial (or those outside not trial not receiving the best treatment) are not explicitly considered. Chick et al [7] and Ryzhov et al [53] discuss how the benefits of these participants can be incorporated into the value-based approach using so-called online learning techniques.
Can the value-adaptive framework handle different types of market exclusivity agreements?	The case study examples assume a fixed size population to benefit from the treatment selection decision. Alban et al [5] illustrates how patent protection periods that decrease in the length of the trial affect the optimal fixed duration length of a value-based trial design.

Does the value-adaptive trial require fully sequential allocation, or can batch allocations of participants be used?	Batch adaptive trials allow for multiple participants to be assigned to multiple treatments in one batch (rather than using pairwise allocations noted in the case study examples). Several methods exist to allocate multiple samples to a finite number of arms using Bayesian expected value of sample information [54,57,60,61].
How can we incorporate our prior information into the value-based approach?	Expert elicitation techniques might be used to assess the requisite prior distributions [46,62]. One can use pilot data and machine learning techniques to inform the choice of prior distribution, even for multi-arm value-adaptive trials [8].
What if bias has been introduced to an adaptive trial?	Bias is a known issue in the analysis of adaptive trials [3]. It has been shown to have effects in health economic analysis of adaptive trials [63]. Existing corrections to adjust for the mean INMB for the patients to be treated can be used in case the trial participant population differs somewhat from the population of patients to be treated post-adoption. Further work should consider how to incorporate bias adjustment of primary and secondary trial endpoints into the value-adaptive calculations.

3 Implications of the value-adaptive design approach for publicly funded research

Through the ENACT project, we have developed the depth and granularity of understanding of the opportunities and challenges of value-adaptive designs for stakeholders across the publicly funded research system. These issues were informed by discussions with key stakeholders from across the NIHR during a workshop in November 2019, as well as by the experiences (both methodological and practical) of the ENACT collaborators. These opportunities and challenges and the implied recommendations and actions are discussed in the next sections.

We consider our discussion in relation to three stages of clinical trials research and common tasks that take place at each stage, based on the "NIHR Clinical Trials Toolkit Route map" [64], as summarised in Table 3:

1. Design and Funding - trial planning and design, funding proposal development, funding panel review.
2. Conduct and Analysis - protocol and trial documentation development, ethics approval, internal pilot, trial management and monitoring, safety monitoring, statistical analysis, health economic analysis, monitoring by funders.
3. Reporting and Implementation - reporting results, health technology assessment and implementation of proven interventions into clinical practice.

We also consider the roles and activities of six important stakeholder groups involved throughout these three tasks; Research Funder; Trial Research Team; Participants and the Public; Clinical Research Delivery in Healthcare Organisations; Health Technology Assessment Decision Makers; and Commissioners and Clinicians. It is also important to recognise the roles of each of these groups in both the implementation of new interventions and in the undertaking of publicly funded research. This cross stakeholder view is highlighted by the joint guidance from the NIHR and NHS England on "baking in" assessment of the value and real world cost of research as part of clinical research projects [65].

Table 3: Summary of NIHR stakeholders and their current roles in the three stages of clinical trials research

	Research Funder	Trial Research Team	Participants and Public	Clinical Research Delivery in Healthcare Organisations	Health Technology Assessment Decision Makers	Commissioners and Clinicians
Design and Funding	Choosing direction of research for funding stream (e.g. commissioning research in specific areas) Allocating funding to research projects	Developing the research proposal Calculating the cost of conducting the clinical trial	Contributing to the design of the trial and its appropriateness Providing patient perspective (e.g. choosing appropriate outcome measures and identifying harms)	Reviewing grant applications and sitting on funding panels		Identifying clinical issues that require researching
Conduct and Analysis	Reviewing trial progress (e.g. using internal pilots with stop-go criteria) Considering funding extension requests	Writing trial documents including protocol, statistics and health economic analysis plans Obtaining ethics approval Monitoring trial progress and safety Identifying sites and randomising participants Preparing data, conducting interim and final analyses	Participating in trials Public involvement in trial conduct and analysis (such as attending trial steering group meetings or specific public advisory group meetings, advising on participant recruitment)	Facilitating the conduct of clinical trials research (e.g. providing research nurses) Recruiting participants Delivering interventions Collecting outcome data		
Reporting and Implementation	Publishing full trial methods and results in comprehensive monograph	Reporting and disseminating trial results (e.g. papers and conferences)	Public involvement in reporting and dissemination Patient acceptance of results		Interpreting trial results for health technology decision making	Implementing changes in practice based on evidence from trial

3.1 Opportunities and challenges for stakeholders

Table 4 sets out an analysis of issues for stakeholders when considering value-adaptive designs.

3.1.1 Design and funding

A key benefit of the value-adaptive approach is the incorporation of health value. As demonstrated in the case studies above, this can be used to help determine whether it is worthwhile conducting the trial at all, whether a fixed sample size design is preferable or whether a value-adaptive design should be used (trial value admittedly may be one of several important criteria for trial funding decisions, others including but not limited to fairness, access, and exploration of new technologies). The opportunity here could help research teams to determine the most appropriate design for their trial and providing an additional justification for their choice [1–3,11].

From a research funder perspective, it is possible that more trials could receive funding within a given budget and timeframe, and the goal of technology adoption by agencies such as NICE is more explicitly considered. A more formal analysis of the potential health gain and value for different intervention-disease areas could also help in prioritising research topics across a portfolio of studies [66]. This could be a portfolio in a particular disease area, or perhaps the diverse portfolio of studies funded by programmes such as the NIHR Health Technology Assessment funding stream.

Funders will be interested in a broader trade-off between the additional administrative/data analysis work to organise and conduct value-adaptive trials and the scale of the expected value obtained by doing so – "how much value is your value-based method expected to create for me, over existing practice?" This will be driven by factors such as the size of the potential population, the potential extent of health improvement, the potential for NHS cost savings and the time horizon for which the evidence will be relevant after the trial is completed [26,30,67–69]. As with other Bayesian approaches, it will be necessary to obtain valid and justifiable prior distributions to describe the key existing uncertainties in the likely trial outcomes before the trial happens. This process has been well discussed in the literature [33]. The evidence to inform current uncertainty in outcomes could come from expert elicitation processes [62], from relevant grey or archival literature, or data from a pilot study [8]. The research funding body could also take the opportunity to invest in funding for short pilot studies as part of providing such prior evidence.

There is a greater requirement to understand and measure the cost of the research process itself, including separating fixed costs from variable costs which accrue during the trial. Additionally, there

is the financial administration and associated management of resources and staff – if the trial does finish earlier, then which costs are saved, where are they redistributed, what happens for the staff allocated to the research project? Sufficient expertise will be required by funding programmes to assess these designs and manage programme budgets more flexibly. Likewise, research teams may need to consider the impact that the value-adaptive design will have on funding their staff who potentially work across multiple concurrent projects and are employed with contracts based on project funding. Although the processes for stopping trials early already exist for NIHR adaptive trials, and indeed for trials which are not adaptive but have to end early, for example when there are problems with recruitment or delivery of experimental interventions. For multi arm trials there is less concern with earlier stopping: one can allocate research costs, if they are sunk, to develop further evidence by randomising to more promising arms.

There is a clear and important role of the UK Clinical Research Networks (CRNs) to share best practice on how to handle spreading resources across the recruitment and retention of trials whose length may change during the study. Additionally, many UK clinical trials units have online randomisation systems [70], that could be developed to work flexibly as data accrues and the value-adaptive calculations are undertaken.

Once a range of designs have been calculated for a trial the whole research team can make an informed decision as to the most appropriate design for the trial. This will consider practical issues such as being able to recruit the required population, staffing concerns as well as financial factors. Members of the public are an important stakeholder group that should not be overlooked. As discussed by Flight et al [71], value-based designs have the potential to change the focus of clinical trials away from the traditional clinical effectiveness viewpoint and this may not be acceptable to the public and potential trial participants. It is recommended that research teams considering a value-based design actively engage members of the public in the design of their research early on.

3.1.2 Conduct and analysis

The primary opportunities arising at the conduct and analysis stage of a trial come in the flexibility of being able to amend the trial dynamically as the data accrues such as stopping early, extending the sampling, changing treatment randomisation, or changing recruitment rates. If value-adaptive trials showing strong evidence that one of the two health technologies is cost-effectiveness are stopped early, resources may be used elsewhere rather than running each trial to its fixed design conclusion. We anticipate that, in practice, any actual decision to stop a trial early will require judgement on a range of factors. For example, the methods set out above for assessing a value-adaptive stopping time

may happen alongside the traditional clinical effectiveness stopping rules for adaptive clinical trials such as the O'Brien-Fleming stopping rule or the Pocock stopping rule [72,73].

For the trial research team, the value-adaptive approach will involve additional work to collect and undertake analysis of the accruing dataset rather than at the end of the trial. These costs were not considered in the case studies reported in this paper. Data to inform the ongoing updating of the health economic analysis and remaining uncertainty in costs and QALYs for each arm of the comparison, and the differences between arms, is needed. In practical terms, this can build on existing data monitoring that already takes place during the trial for clinical outcomes and health economics when analysed at the end of a fixed design trial. This would almost certainly increase the budget for data management and analysis during the trial compared to a fixed trial. It is important to remember, that the value-based framework considers these additional costs of conducting the value-adaptive design and it might be that the optimal design choice, balancing the costs and benefits of each design, is the fixed sample size design.

3.1.3 Reporting and implementation

As with all research, the methods and results will need to be reported in an understandable way to all stakeholders with clear sections reporting the value-adaptive approach taken. Report reviewers and referees of the associated journal articles will need to understand the value-adaptive methods and therefore some training will be necessary. Our ENACT project has worked on two case studies that add to the available worked examples and associated open source code to facilitate this [49,50,74]. Additionally, reporting guidelines for adaptive clinical trials can be applied where relevant [2].

It is important to emphasise the crucial work of the Academic Health Service Network (AHSN) and analogous agencies in diffusing innovations in complex systems [75]. There could be a risk that if a trial has stopped early, the result might be interpreted differently by practising clinicians who might be more familiar with longer fixed sample size design trial evidence. This could make them more reluctant to implement findings of value-adaptive designs that have terminated early. Communication to the clinical community by key opinion leaders could be important here.

Table 4: Opportunities (green boxes) and challenges (blue boxes) of value-adaptive designs for key stakeholders during the healthcare research and decision-making process

	Research Funder	Trial Research Team	Participants and Public	Clinical Research Delivery in Healthcare Organisations	Health Technology Assessment Decision Makers	Commissioners and Clinicians
Design and Funding	More trials undertaken for fixed budget due to potential savings	Innovative and efficient trial design more competitive when limited funding				
	Greater alignment between research spend and its value (i.e. population level health gain vs NHS cost savings)	Justification of design using value-adaptive approach	Greater alignment between research spend and its value (i.e. population level health gain vs NHS cost savings)		Value explicitly accounted for in research designs	Identify priorities in terms of large potential health gains or large current budget demands
	Flexibility in planned budget required and clear decision processes for stopping trials needed	Flexibility in planned budget required and clear decision points needed (receive less funding for some trials and more for others)		Commit to more flexible resourcing and possible early stopping		
	New methods expertise (and possibly more time) for committees and peer reviewers will be needed	Grant writing will require more technical work and more expertise to specify and justify proposed design	Participant & public involvement will require a greater understanding of technicalities of design			
Conduct and Analysis	More efficient / flexible trial is undertaken	Reanalyse the position if recruitment or event rates or outcomes are different to the original plan	Participants not in the trial for any longer than necessary	Easier to reach key performance indicators i.e. target sample size		
	Can flexibly extend the trial sample / duration if more information would be valuable	Can flexibly extend the trial sample / duration if more information would be valuable	Fewer trial participants receive ineffective treatment			
	Potentially more work per trial to review interim analyses & agree adaptations					
		Flexible increase / decrease funding & flexible staffing				
Reporting and Implementation	New treatments that are effective and cost-effective get into the NHS more quickly					
	Require explanation of the methods and results in an understandable way					
		Trial report will need comprehensive details on the value-adaptive methods used to inform the design and conduct		Plan for re-using resources if trial stops early or extra resources if trial continues		The results might be interpreted differently by clinicians in practice if the trial has stopped early, which might affect implementation.
		Journal articles of trial results will need journals and peer reviewers to understand methods				

4 Actions and recommendations

The use of value-adaptive designs may bring benefits discussed above. Accruing those benefits in an application may involve changes to some of the activities and actions of the key stakeholders (see Table 5). This reflects many of the recommendations reported by Blagden et al, in relation to the effective delivery of complex and innovative designs [76] and reflects the important work of Jaki and Dimairo et al who consider why the update of adaptive approaches lags behind their methodological development [77,78].

4.1 Funding research studies

Research funders are in a strong position to take leadership in moving forward initiatives for greater use of value-adaptive designs. An indication that the funder welcomes value-adaptive trial applications would incentivise researchers to develop such applications. This could be a funding call that sets out a requirement to undertake a pilot study to obtain information to inform the prior probability distributions for use in the value-adaptive design and encourages the use of this innovative design where appropriate.

Research funding bodies could usefully provide guidance for researchers on how to set out the plans for a value-adaptive trial in research proposals. Adaptive trials are already being funded, and as the value component becomes a part of practice, the proposals for the statistical analysis plan and health economic (and decision modelling) analysis plan should be clear on how the value-adaptive analysis will be undertaken. Training and access to experts who have a more in depth understanding of the methods including adaptive clinical trial designs, Bayesian decision theory and dynamic programming will help funding bodies to assess their appropriateness and accuracy.

Once a value-adaptive trial is running flexible budget management will facilitate the implementation of the approach. There is already a degree of flexibility in the systems for existing trials such as those which stop early through recruitment difficulties or require an extension to their research completion deadline. When a trial stops early, for example, the funding panel chair and programme manager may need to work with research teams to agree on the financing and return of resources to the NIHR.

4.2 Planning and conducting research studies

As with all trial designs, stakeholders such as trial teams and members of the public should contribute to the value-adaptive design. This may include early engagement with regulators and health

technology assessors to ensure the proposed design meets their requirements. Again, access to experts who have an in depth understanding of the methods including adaptive clinical trial designs, Bayesian decision theory and dynamic programming and the relevant software for implementing these methods will facilitate this.

A health economic model may be required earlier in the research process compared to existing practice. It is important also to properly develop the costing for the adaptive trial design so that appropriate funding can be requested, and the value-adaptive approach can be implemented accurately. Work on how to do this is ongoing as part of the 'Costing Adaptive Trials' project [79]. Once a trial is running, flexibility may also be required by research teams who manage staff contracts based on funding from a trial that may stop early or continue for longer. Negotiations and framework agreements for different circumstances between the funder and the research teams that consider the continuity of staff contracts, and the retention of experienced staff will be useful.

During a trial there will be changes to the reporting and communication between the funding body and the trial research team to inform decision making on the progress and adaptations made to the trial. The funding body and data monitoring and ethics committee (DMEC) will need to receive reports on trial progress at specified points and make decisions on whether to adapt the study. The trial team will need to undertake and report pre-specified analyses. When the trial reaches its conclusion the DMEC, trial management group and trial steering committee will all need to agree and approve the finalised analysis and reasoning for criteria to end the trial given the available evidence. The CRN will also need to work out how to move resources such as research nurses to other studies. It is important to note, however, that this is not unique to value-adaptive designs, and many of these processes are in place for adaptive designs and for safety monitoring of fixed sample size designs.

4.3 Reporting and health technology adoption

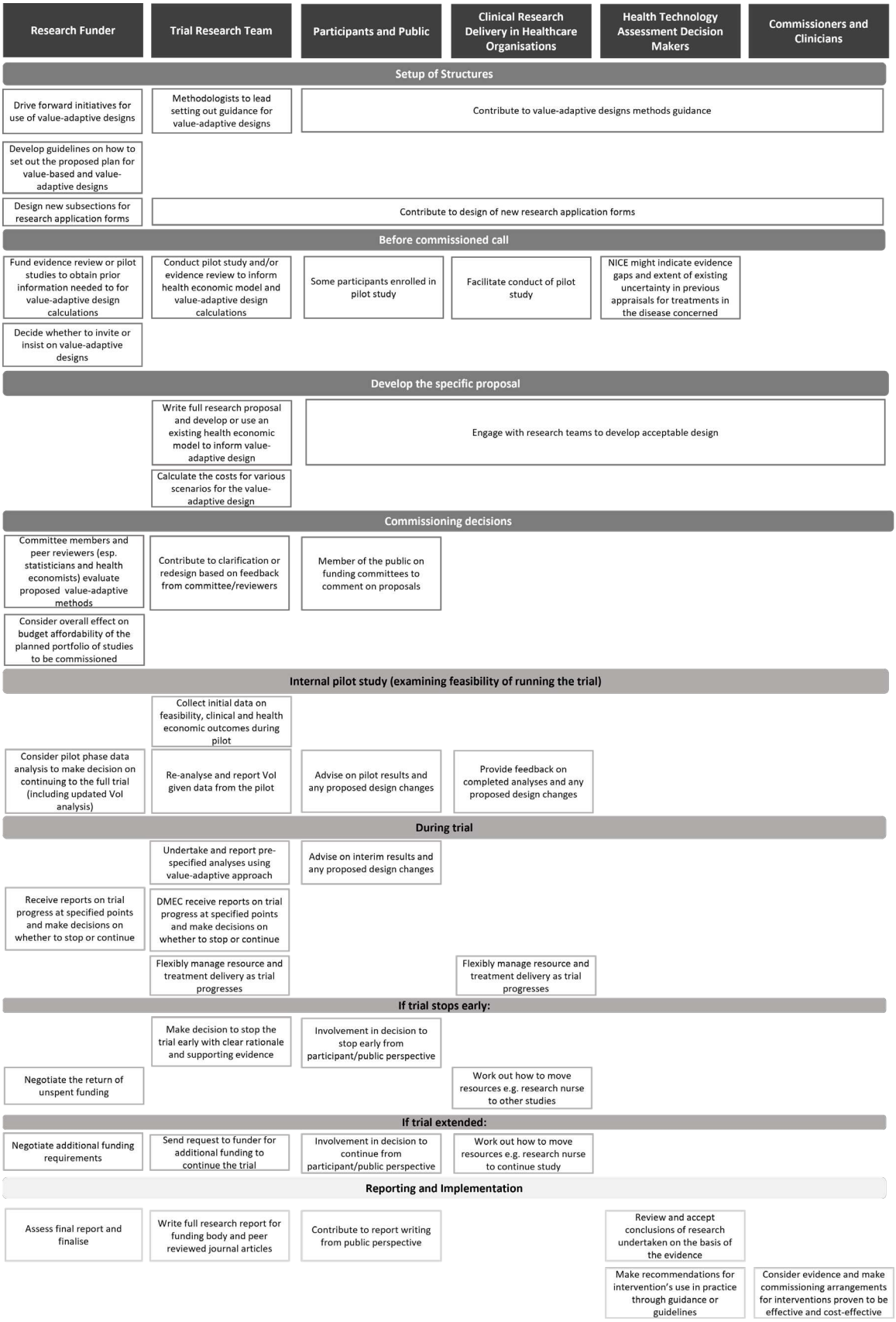
The final reporting of the trial and the use of its final evidence in health technology assessment and clinical commissioning will have very little difference from current practice. The full research report for funding body and peer reviewed journal articles will follow the usual processes, as will the referring and final assessment from the funding body. Health technology assessment decision makers are already set up and will consider the evidence and make recommendations for an intervention's use in the NHS such as through NICE guidance or guidelines. Commissioners of health services and clinicians will consider that evidence and decide to implement the use of any interventions proven to be effective and cost-effective.

When reporting the result of a value-adaptive trial it will be important that all stakeholders (patients, clinicians, funders, health technology assessors) are able to understand the approaches taken, critically assess this and appraise the impact it will have on results. This will require careful presentation by research teams, much like when reporting results for traditional clinical trials. Relevant aspects of the Adaptive designs CONSORT Extension may facilitate this [2].

5 Conclusions

Value-adaptive clinical trial designs attempt to address the need for more efficient, faster and innovate approaches to clinical trial design by providing rules for making changes to clinical trials as they are being conducted, based on an assessment of the cost-effectiveness of the research process itself. This can include stopping the trial early, changing the fraction of participants allocated to the arms, or other adaptations that help efficiently identify the alternative treatment with the best value for the population that benefit from the health technology assessment. This paper sets out the key methods involved and assesses the opportunities and challenges which arise for publicly funded research using the UK NIHR as an exemplar. Many of the systems and processes to deploy value-adaptive designs already exist, and with increased experience and application of these approaches there is great promise for more efficient publicly funded health research. These methods can be adapted in part in privately funded applications, though additional work may be useful for incentive alignment and other issues that arise in that multi-stakeholder environment.

Table 5: Mapping of the Potential Activities of NIHR stakeholders to move to implementing these methods during the healthcare research and decision-making process DMEC; Data monitoring and ethics committee



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Funding statement: This work is part of the EcoNomics of Adaptive Clinical Trials (ENACT) project, which is funded by the National Institute for Health Research (NIHR) CTU Support Funding scheme. The CACTUS Pilot trial was funded by the NIHR under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-1207-14097). This study was also supported by the Stroke and Telehealth themes of the South Yorkshire Collaboration for Leadership in applied health research and care (CLAHRC). NIHR CLAHRC for South Yorkshire acknowledges funding from the NIHR. The study also received support from North of Tyne PCT. The Big CACTUS project was funded by the NIHR Health Technology Assessment Programme (12/21/01). Additional funding support was provided by the Tavistock Trust for Aphasia. The views expressed are those of the author(s) and not necessarily those of the National Health Service, NIHR or the Department of Health and Social Care Health Technology Assessment Programme, the Tavistock Trust for Aphasia, or the Stroke Association. The HERO trial was funded by Arthritis Research UK (now Versus UK) and sponsored by the University of Leeds, with York Trials Unit as UKCRC-registered CTU. The views expressed are those of the author(s) and not necessarily those of the National Health Service, NIHR or the Department of Health

and Social Care Health Technology Assessment Programme, the Tavistock Trust for Aphasia, or the Stroke Association.

Acknowledgements: SC acknowledges the support of the Novartis Chair in Healthcare Management at INSEAD. We would like to thank the following for their contribution to the ENACT project as collaborators and/or workshop attendees: Stephen Brealey[2], Cindy Cooper[6], Belen Corbacho[2], Steve Goodacre[1], Phil Jennings[4], Ada Keding[2], Stephen Lock[5], Paolo Pertile[3], Sarah Ronaldson[2], Charlie Welch[2]. We would also like to thank Andres Alban[7] for comments on the earlier drafts of the paper.

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Competing interests

The authors have no conflicts of interest.