**Value-based Adaptive Clinical Trial Designs for Efficient Delivery of NIHR Research**

EcoNomics of Adaptive Clinical Trials (ENACT)

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# Abstract

A value-adaptive clinical trial analyses accumulating data on the costs of research, the precision of the estimated effectiveness of a treatment and the health technology assessment decisions around cost-effectiveness, to inform changes to the trial. These designs have the potential to provide more efficient, faster and innovative studies that give robust evidence to inform practice and policy. The EcoNomics of Adaptive Clinical Trials (ENACT) project aimed to 1) increase the number of experts trained in the methodology of a specific kind of value-adaptive design known as a value-based sequential clinical trial, 2) improve existing understanding of the methodology’s strengths and weaknesses by assessing its feasibility for the delivery of more efficient NIHR-funded research, and 3) provide practical resources that support implementation of such methods. Key outputs from this project are available via the [ENACT webpage](https://www.sheffield.ac.uk/scharr/research/centres/ctru/enact) (1).

#  Introduction

An adaptive design analyses accumulating data, at pre-specified time points during a trial, to inform changes to the trial, such as changing its length or varying a drug’s dosage. These designs aim to improve the efficiency of clinical trials by saving financial resources, preventing patients from being needlessly randomised and bringing better treatments to patients sooner (2–4). The National Institute for Health Research’s (NIHR) support of the delivery of innovative clinical trials, including adaptive designs, is evident through studies such as the STAMPEDE trial (5) and the Randomised Evaluation of COVID-19 Therapy RECOVERY trial (6), as well as through its 2019 Clinical Trials Unit (CTU) Support Funding call (7).

In the UK, we have limited resources for funding treatments on the NHS. The National Institute for Health and Care Excellence (NICE) are required to make recommendations about which treatments should be adopted into practice. To do this they consider the ‘value for money’ offered by a new health technology (such as a new drug or other treatment (8)), accounting for both its benefits and costs. The same idea of value may be used to prioritise and design health research, using so-called ‘value of information’ methods to inform more cost-effective research (9–11). A value-based approach to designing clinical trials incorporates the costs and benefits of the research process itself. However, adaptive designs rarely consider value in their design and analysis (7). The emerging methods of value-adaptive designs combine elements of both the value-based and adaptive approaches (12–15).

In the ENACT project, we have focused on a type of value-adaptive design known as the value-based sequential design that was developed Chick et al. (2017) (12) and Alban et al. (2018) (13). This innovative design is based on a Bayesian decision-theoretic model whose stopping rule is informed by an assessment of the cost-effectiveness of the research process itself. The model stops recruitment to the trial when the expected costs of continuing exceed the expected benefits.

By engaging with stakeholders from across the NIHR, the ENACT project aimed to

1. increase the number of experts trained in the methodology of value-based sequential designs,
2. improve existing understanding of the methodology’s strengths and weaknesses by assessing its feasibility for the delivery of value-adaptive NIHR-funded research,
3. provide practical resources that are required to support implementation of the methodology.

Key outputs for CTUs from the ENACT project include

* **Output 1 -** Discussion paper for a non-technical audience that considers the strengths and weaknesses of the value-adaptive approach in the context of NIHR-funded research.
* **Output 2 -** Report of the retrospective application of the value-based sequential design to two case studies (Big CACTUS and HERO). These will be authored by members of CTUs who have been trained as part of the ENACT project (see Output 4 below).
* **Output 3 -** Recommendations for the practical considerations for CTUs when considering the use of value-based sequential designs.
* **Output 4 -** Training course that covers the fundamentals of Bayesian decision theory and value-based fixed and sequential clinical trials that can be developed for the training of further CTUs.
* **Output 5 -** [Webpage](https://www.sheffield.ac.uk/scharr/research/centres/ctru/enact) that collates relevant resources for value-adaptive clinical trials (including the ENACT outputs 1-3).

# Methods and Results

The ENACT project was divided into four deliverables. The methods and results of Deliverables 1 to 3 are outlined in this section. Deliverable 4 is discussed in Section 4.

## Deliverable 1 - Interdisciplinary knowledge integration

A two day workshop for the ENACT collaborators (listed in Section 5), hosted by the School of Health and Related Research (ScHARR), was held at the University of Sheffield on the 25th and 26th November 2019. The workshop provided attendees with a broad background in the methodology required to implement value-adaptive designs and, in particular, the value-based sequential design. The full workshop agenda is given in Appendix 8.1. The sessions allowed ENACT collaborators to share their own research expertise, including theory-based topics such as adaptive and value-based approaches to clinical trial design and practical perspectives from trial managers. Day 2 of the workshop focused on how the methods would be applied to the case studies of Deliverable 3 (see Section 2.3).

To ensure that the CTU teams from Sheffield and York were sufficiently trained in the methods required for applying the value-based sequential design to the case studies, a mini course was organised to cover the fundamentals of Bayesian decision theory and value-based fixed and sequential clinical trials (Output 4). This content was designed to match the case study teams’ needs for training. The course outline is available in Appendix 8.3. The course was delivered over a series of six two hour online classes. This can be used as a template for similar training courses for further CTUs.

A key success of the ENACT project has been increasing the number of CTU researchers with an understanding of the theory of value-based sequential designs. This has focussed initially on York Clinical Trials Unit and Sheffield Clinical Trials Research Unit, with resources and materials developed and piloted on this sample of researchers. However, these materials can now be extended to all CTUs to further increase the knowledge base of value-based sequential designs across the UK.

## Deliverable 2 - Understanding of the methodology’s strengths and weaknesses

A second workshop, also hosted by ScHARR, was held at the University of Sheffield on the 27th November 2019. This workshop brought together stakeholders from across the NIHR and a subset of the ENACT collaborators to discuss when and where value-adaptive methods could be applied when commissioning NIHR trials and how decisions about early termination/late running could be made (full agenda given in Appendix 8.2). The attendees were given an introduction to the aims of the ENACT project and summaries of key concepts. Discussions covered topics such as perspectives on “efficiency” and “value of evidence”, the use of adaptive designs in current practice and perceived barriers for their funding, conduct and implementation. Discussions also considered practical aspects and the information needed for value-adaptive methods to be used routinely in the NIHR. Detailed minutes from this meeting have been used to inform the drafting of Output 1, written for a non-technical audience.

Following these discussions, it was felt that many of the systems and processes required to deploy value-adaptive designs within the infrastructure of the NIHR already exist, and with increased experience and application of these approaches there is potential for making publicly funded health research more efficient. Opportunities provided by the methods for stakeholders (such as research funders and health technology assessment decision makers) include explicitly considering the ultimate treatment adoption decision when designing and conducting adaptive trials as well as adding to the toolkit available to research teams when choosing and justifying their choice of trial design.

Challenges identified in the second workshop include the perceived learning curve of stakeholders to understand the value-adaptive approach when applying for research funding and disseminating trial results. Additionally, the impact of the designs on the financial administration of funder budgets and staff in CTUs when trials may be shortened or lengthened was raised as requiring careful thought. The ENACT outputs provide one step towards lessening this learning curve. It was also noted in the workshop that many trials currently stop early due to recruitment issues, or require extension. Hence similar performance management processes could be adapted for the implementation of value-adaptive designs.

We feel that research funders, supported by experts in value-adaptive methods, are in a strong position to move forward initiatives for the increased use of these designs, perhaps through specific commissioned calls in the first instance. To facilitate this, they are likely to need to provide guidance for researchers on how to set out their plans for a value-adaptive design in their research proposals and training for funding panel members and reviewers to ensure they are aware of, and familiar with, these methods. The ENACT outputs can be used as a starting point for this training. Clinical trials teams will need to engage with all stakeholders, including the public, when designing a value-adaptive trial and consider carefully the resources required to implement successfully this approach. They will also need to ensure the validity and integrity of the trial is maintained, with sufficient pre-specification of analyses and expertise on trial committees, such as data monitoring and ethics committees (DMEC).

## Deliverable 3 – Retrospective case studies

Deliverable 3 aimed to

1. Apply the Bayesian value-based sequential model of Chick et al. (2017) (12) and Alban et al. (2018) (13) to two new retrospective case studies - the Hydroxychloroquine Effectiveness in Reducing symptoms of hand Osteoarthritis (HERO) study (16) and the Cost-effectiveness of Aphasia Computer Treatment Compared to Usual Stimulation (Big CACTUS) trial (17–19).
2. Compare the estimated health and economic value provided by the value-based sequential design with
	1. the original, frequentist, fixed sample size design,
	2. a fixed sample size design which maximises the expected net benefit of sampling (the ‘value-based one stage design’) (20).
3. Add to existing knowledge by exploiting special features of the Big CACTUS and HERO studies, including the use of prior information, a health economic modelling approach, and the use of methods to deal with missing data.
4. Contribute to a summary of the procedures that CTUs could follow if they are considering using the value-based sequential design in future trials.

Output 2, a report presenting the preliminary results from the two case studies includes recommendations for the practical considerations for CTUs (Output 3).

The case studies present simple procedures for comparing the different designs prior to a trial taking place, thereby giving an indication of the performance of the value-based sequential approach relative to that of the other two designs. Performance characteristics included the expected sample size of the trial, its expected cost, the overall expected value delivered to the healthcare system and the probability that the trial concluded that the one of the two treatments of interest was cost-effective.

Results showed that no one design performed best in all performance characteristics, with reasons for differences in performance being determined by the precise characteristics of the trial under consideration. For example, sequential trials in which the time to follow-up comprises a large proportion of the overall recruitment period (as in the CACTUS and HERO case studies) may provide less potential for delivering value than trials when the follow-up period is a smaller proportion. This is because patients have already been recruited to the trial – and research costs committed – by the time interim analyses to inform the value-based sequential model start. In contrast, trials with a good overlap between observing accumulating data and continuing recruitment may generate value when one treatment is clearly superior to the other on cost-effectiveness grounds. This was demonstrated in the only existing application of the value-based sequential design prior to the ENACT project (21). The ENACT project’s results suggest that there is little advantage when there is an equivocal cost-effectiveness signal from the trial. This was illustrated by the HERO case study, where the difference in effectiveness and cost between the two technologies was negligible, resulting in a trial which was almost equally likely to conclude in favour of the intervention or placebo.

# Conclusions

The ENACT project has engaged stakeholders from across the NIHR, including those from CTUs, to build capacity for the use of value-adaptive designs in NIHR-funded clinical trials. We have produced outputs that address the unmet need for training, applying and implementing these designs. This includes a discussion paper highlighting the methodology’s strengths and weaknesses (Output 1), two new applications of the methods (Output 2, CACTUS and HERO case studies), a chapter detailing practical considerations for CTUs to follow when considering using a value-based sequential design (Output 3) and a training course that can be further developed to train more staff in CTUs (Output 4, Appendix 8.3).

The project has also identified key areas for further research, including the need for further retrospective case studies, the potential to deploy the approach prospectively in an exploratory capacity, extending current case studies to consider other adaptive designs such as multiple arm trials, and issues including subgroup analyses and non-linear recruitment rates.

Challenges to deployment of such designs remain, but with increased experience and application of these approaches we hope they can be implemented, where appropriate, with potentially only small changes beyond current practices. If CTUs decide the value-based sequential approach is appropriate they will need to draw on existing recommendations for implementing adaptive designs and value-based designs (2,4,10,11,22). In addition, they must ensure that they have access to appropriate expertise in the value-based sequential methods, can accurately calculate the costs of conducting the trial and are able set up appropriate computing and management processes to implement the design successfully.

With careful implementation, the future use of value-adaptive designs holds promise for more efficient publicly funded health research. The ENACT project has successfully laid the foundations and capacity to support a future larger-scale funding proposal which, it is hoped, will evaluate the model prospectively, alongside existing decision-making criteria, in a future clinical trial.

# Dissemination (Deliverable 4)

Outputs from the ENACT project are available at <https://www.sheffield.ac.uk/scharr/research/centres/ctru/enact>. This webpage will be updated as the project outputs are made available.

To increase awareness of value-adaptive designs beyond the ENACT team, we plan to disseminate our work, with a particular focus on reaching different parts of the NIHR infrastructure.

The ENACT work was presented as part of NIHR Clinical Research Network Virtual Symposium: Delivering Complex and Innovative Design (CID) Studies. LF (ENACT collaborator from Sheffield) presented a summary of value-adaptive designs and the tools and support being developed as part of the ENACT project and took part in a question and answer session on toolkits for complex and innovative trial designs (23).

The ENACT work will be presented at the UKCRC Statistics Operational Group Meeting in April 2021. CW (ENACT collaborator from York CTU) will present a summary of value-adaptive methods and a summary of findings from the HERO case study.

Results from Deliverable 3 have been submitted for presentation at the annual conference of the Royal Statistical Society by MF (ENACT collaborator from the Department of Economics, University of York, and the Department of Statistical Sciences, University of Bologna).

During 2021 and 2022 we plan to disseminate the findings further including; publication of the discussion paper (Output 1) and case study results (Output 2) in peer reviewed journals and presentation of ENACT outputs at the International Clinical Trials Methodology Conference.

We also plan to host a dissemination workshop that will provide an overview of the methodology and include reports from the case studies and trial managers showing how the methodology may assist the efficient delivery of NIHR research. The workshop will be aimed at stakeholders from across the NIHR, including CTU staff.

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* The HERO trial sponsor for sharing necessary expenditure summaries. Members of the HERO trial team who were directly involved in the ENACT project (AK, SR, BC, PT).

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Ethics approval for the secondary use of data was granted by the ScHARR research ethics committee (ref: 032229).

The views expressed are those of the authors 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.

## List of collaborators

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Professor Paolo Pertile (PP), Professor of Public Economics.

## Contribution of collaborators

AB, SC, LF, MF formed the project management group and provided strategic oversight and direction to the whole project. Contributions of the ENACT collaborators at the Workshop 1 are given in Appendix 8.1. The workshop was attended by LF, SAJ, AB, SB, BC, AK, SR, PT, CW, MF, SC, PP. Contributions of the ENACT collaborators at Workshop 2 are given in Appendix 8.2. This workshop was facilitated by AB and attended by LF, SAJ, PT, MF, SC, and PP. MF developed and delivered the mini course. This was attended by LF, AK, BC, SR, and CW. LF and PT organised the ethics approval for the CACTUS and HERO case studies respectively. The project management group provided strategic oversight to the case study analysis and report writing. The CACTUS case study was led by LF with support from MF, SAJ, CC and the Big CACTUS trial team. The HERO case study was led by MF with support from CW, AK, PT, BC and SR. LF, MF, BC, AK, SR, PT, PT, CW, AB, SC contributed to the writing of the case study report which was reviewed and feedback provided by CC, SAJ and the CACTUS trial team on the introduction and CACTUS chapters. The discussion paper was drafted by the project management group and shared with Workshop 2 attendees and CC for feedback. LF prepared a draft of this report that was reviewed by all collaborators.

# Conflict of interest declaration

There are no conflicts of interest.

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# Appendices

## Agenda from Workshop 1 held at the School of Health and Related Research, University of Sheffield.

Day 1: 25/11/2019

|  |  |  |
| --- | --- | --- |
|  | **Topic** | **Presenter** |
| 09.30–10.00  | Welcome and Introductions | SAJ |
| 10.00–10.30 | Outline of Workshops 1 and 2 | MF, LF |
| 10.30–10.45 | Coffee |  |
| 10.45–11.45  | Overview of adaptive clinical trials  | SAJ |
| 11.45–12.45  | 1. Value-based Bayesian decision-making for clinical trials. 2. The economics of sequential value-based designs. | PP, MF |
| 12.45 –13.30 | Lunch |  |
| 13.30–14.40 | 1. Application of value-based and VoI methods in clinical trials. 2. Making a value-based clinical trial fully sequential.  | AB, SC |
| 14.40–15.40 | The trial manager’s perspective: ProFHER | SB |
| 15.40–16.00 | Tea |  |
| 16.00–17.00 | The trial manager’s perspective: NHS England/NIHR  | PT |
| 17.00–17.15 | Summary |  |

|  |  |  |
| --- | --- | --- |
|  | **Topic** | **Presenter** |
| 09.00–09.15 | Overview of day 2 |  |
| 09.15–10.15 | Case study 1: Big CACTUS  | LF |
| 10.15–10.30 | Coffee |  |
| 10.30–11.30 | Case study 2: HERO | PT, SR |
| 11.30–12.30 | The Chick et al./Alban et al. model applied to the ProFHER pragmatic trial  | MF |
| 12.30–13.15 | Lunch |  |
| 13.15–14.30 | Applying the Chick et al./Alban et al. model to the case studies | ALL |
| 14.30–15.30 | Introduction to the Matlab code for solving the Chick et al./Alban et al. model  | SC |
| 15.30– 15.45 | Tea |  |
| 15.45–16.45 | Management of project. Key milestones and deliverables | ALL |

Day 2: 26/11/2019

## Agenda from Workshop 2 held on 26/11/2019 at the School of Health and Related Research, University of Sheffield.

|  |  |  |  |
| --- | --- | --- | --- |
| **Time** | **Session** | **Description** | **Speaker** |
| 10:00-10:15 | Coffee  |
| 10:15-10:25 | Introductions | BackgroundAims of ENACTAims for the dayGround rules | LF |
| 10:25-10:45 | Discussion | How are the NIHR and NHS England quotes aligned to your perspectives?What is your view of “efficiency”?What is your view of “value of evidence”? | PT/Stakeholders |
| 10:45-10:55 | Current state of play  | Longer term aims Specific aims of ENACT | SC |
| 10:55-11:05 | Adaptive Designs | Introduction to adaptive designs  | SAJ |
| 11:05-11:25 | Discussion | As adaptive designs run at the moment what are the issues/ barriers focussing on funding, conducting and implementing research? | SAJ/stakeholders |
| 11:25-11:40 | Coffee |
| 11:40-11:50 | Value based adaptive designs  | Overview of value based methodsProFHER case study  | MF/PT |
| 11:50-12:45 | Discussion  | * + 1. Perspectives on value based adaptive designs
 | PT/stakeholders |
| 12:45-13:30 | Lunch |
| 13:30-13:40 | Briefing document and position paper  | Aims of paperTitle/structure  | SC |
| 13:40-13:50 | Introduction to discussions | Thinking time ahead of discussions  | ALL |
| 13:50-14:40 | Discussion – practical  | What are the practical consideration of value based adaptive designs in the funding, conducting and implementation of research Who are the stakeholders and what will they do?What information do they need?What are the parts of the infrastructure that we need to engage with What are our current blind spots? | SAJ/stakeholders |
| 14:40-15:00 | Coffee |
| 15:00-15:20 | Summary of discussions | What are our key points so far?  | LF |
| 15:20-16:00 | Further discussion |   | AB/Stakeholders |
| 16:00-16:30 | Next Steps |  | LF |
| 16:30  | Meeting close |  |  |

## Mini-course outline

The ENACT Project Mini Course:

Methods for Value-Based Bayes Sequential Trials

Outline

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*For the NIHR ENACT project*

*1st October 2019–30th September 2020*

March 10, 2021

*Special thanks to Charlie Welch, York Trials Unit, University of York, for his detailed comments and feedback on the lecture slides.*

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*Sheffield, and Belen Corbacho, Ada Keding, Sarah Ronaldson and Charlie Welch, York Trials Unit, University of York, for their online participation, comments and feedback.*

# Aims and objectives of the mini course

1.1 Aims

To provide the trials unit teams involved in the ENACT project with sufficient knowledge of Bayesian sequential, decision-theoretic models to apply the methodologies to the two case studies – HERO and Big CACTUS – that form Deliverable 3 of the project:

‘The methods employed in Forster et al. (2019) will be applied to two case studies – ‘Big CACTUS’ and ‘HERO’ – to: (a) identify how the model of Chick et al. (2017) may be deployed in new contexts; (b) prepare a document outlining the procedures CTUs should follow when implementing the approach in future trials.’

1.2 Objectives

By the end of this mini-course, you should be able to:

1. explain the difference between Frequentist and Bayesian inference for clinical trials
2. explain Bayes’ rule and use it to update a prior distribution for a parameter to obtain a posterior distribution
3. explain the principles of dynamic programming and why adding interim analyses to a clinical trial can have value
4. explain the main Bayesian decision-theoretic approaches to value-based clinical trial design (one-stage, two stage (one interim analysis) and fully sequential)
5. be able to run Matlab code to obtain a value-based stopping policy for the HERO or Big CACTUS case studies
6. Timetable and locations

The course is taught online and comprises six lectures in total. Join in whenever you wish.

* Friday 20th March 2020, 10.00–12.00 and 13.00–14.45. Classes 1A and 1B: Overview and basics of Bayesian inference , Bayesian inference for normal distributions
* Thursday 23rd April 2020, 12.00–14.00. Class 2A: Decision theory and value of information
* Friday 24th April 2020, 12.00–14.00. Class 2B: Value of information for normal prior, normal likelihood models
* Thursday 30th April 2020, 12.00–14.00. Class 3A: Dynamic programming
* Monday 17th August 2020, 12.00–14.00. Class 3B: Value-based sequential clinical trial designs
1. Class slides and learning objectives

Class 1

1A Overview and basics of Bayesian inference 1B Bayesian inference for normal distributions

By the end of Class 1A you should be able to:

1. explain the difference between Frequentist and Bayesian inference
2. explain how Bayes’ rule works
3. apply Bayes’ rule for the case of a binary parameter and binary data

By the end of Class 1B you should be able to:

1. use data from a sample to update a normal prior distribution using Bayes’ rule and a normal likelihood to obtain a normal posterior distribution
2. explain the meaning of a conjugate prior
3. explain how Bayes’ rule can be used to make forecasts

Class 2

2A Decision theory and value of information

2B Value of information for normal prior, normal likelihood models

By the end of Class 2A you should be able to:

1. explain the main components of a decision-theoretic model and why information has value
2. explain how closed loop and open loop control methods may be used to calculate the expected value of perfect information

By the end of Class 2B you should be able to:

1. explain the meaning of, and be able to calculate, the expected value of perfect information for a normal prior–normal likelihood model
2. explain the meaning of, and be able to calculate, the expected value of sample information for a normal prior–normal likelihood model
3. define and be able to calculate the expected net benefit of sampling

Class 3

3A Dynamic programming

3B Value-based sequential clinical trial designs

By the end of the Class 3A you should be able to:

1. apply calculations for EVPI, EVSI and ENBS to the case study
2. explain why adding an interim analysis to a CEA carried out alongside a clinical trial can add value

By the end of the Class 3B you should be able to:

1. explain how the dynamic programming algorithm is used to solve the value-based sequential model of Pertile et al. (2014) and Chick et al. (2017)
2. interpret the stopping boundaries from the model in the light of accumulating data on cost-effectiveness
3. with the help of Chick’s lecture notes from Workshop 1 of the ENACT course, be able to run the Matlab code with parameter values of choice to obtain the optimal stopping boundaries for the value-based sequential design
4. Reading, web links etc.
	1. General reading

Good key texts on Bayesian statistics are Lambert (2018) and Kruschke (2015). Advanced texts on Bayesian decision theory are DeGroot (1970) and Raiffa and Schlaifer (1959). References to published articles will be made in the class slides.

* 1. Web links

Ben Lambert (textbook cited above) has a nice website with materials which supplement the lectures: <https://ben-lambert.com/bayesian/> John Kruschke has a blog with lots of interesting articles: <https://doingbayesiandataanalysis.blogspot.com/>

References

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Raiffa, H. and Schlaifer, R. (1959). *Probability and Statistics for Business Decisions*. McGraw Hill, New York, First edition.