Heggie, Robert (2023) Incorporating implementation within the economic evaluation of health technologies

Robert Heggie

M.A. (Hons), M.Sc.

Submitted in fulfilment of the requirements of the Degree of Doctor of Philosophy

Health Economics and Health Technology Assessment (HEHTA)

School of Health and Wellbeing

College of Medical, Veterinary and Life Sciences

University of Glasgow

February 2023

Scientific summary

Background

Delayed or insufficient implementation of clinically effective and cost-effective health technologies leads to poorer health outcomes for patients and the sub-optimal use of scarce resources for national health services. Several studies have estimated an average lag of approximately 17 years from research findings to clinical practice, with one study finding that only about half of evidence-based practices ever reach widespread use in clinical practice. The issue of implementation has recently been highlighted as a priority for the National Health Service (NHS), while the Medical Research Council (MRC) recommends that implementation be incorporated within the development and evaluation of complex interventions. However, many clinically effective and cost-effective health technologies still fail to achieve optimal implementation in routine clinical practice. One of the most commonly cited barriers to implementation is a lack of evidence on the cost and value of potential implementation strategies. Despite this, implementation is not routinely considered alongside the economic evaluation of health technologies.

Aim

The aim of this thesis is to demonstrate the value of considering implementation within the economic evaluation of health technologies.

Objectives

1. Undertake a rapid systematic review of how implementation has been incorporated within the NIHR HTA programme in the UK.
2. Undertake a systematic review to identify and describe which methods are currently available for incorporating implementation considerations within the economic evaluation of health technologies.

3. Demonstrate how the Value of Implementation framework can be utilised to provide more useful evidence for decision-makers using two case studies.
    3.1. In the context of mechanical thrombectomy for acute stroke in the UK.
    3.2. In the context of venous access devices for the delivery of anti-cancer therapy in the UK.

Methods

Four linked research studies were undertaken, using a multi-methods approach. I undertook two systematic literature reviews to assess the current use and availability of implementation methods in the economic evaluation of health technologies. I then used two case studies to demonstrate how implementation can be incorporated within the economic evaluation of health technologies.

We undertook a rapid review, using a systematic approach, to establish how implementation has hitherto been incorporated within health technology assessment research in the UK. I reviewed studies funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme between the years of 2014-2020 which considered the issue of implementation. To assess how implementation had been incorporated within these studies, I used the Proctor et al. (2012) checklist which provides guidance to researchers planning an implementation study. This checklist contains a list of criteria which the authors recommend should be addressed within a study which aims to evaluate implementation. I also identified a range of themes relevant to implementation, but which were not captured within the Proctor checklist. Finally, a narrative synthesis was undertaken using the key themes identified in this review to evaluate and discuss how implementation had been incorporated within these studies.

I then undertook a second systematic review to identify and describe any methods which are currently available for incorporating implementation within the economic

evaluation of health technologies. A content analysis was employed to organise and identify common themes or “approaches” in the methodologies identified in the review. I described what methods were available, how these methods differed from one another, when they should be used, and where there are gaps remaining.

My first case study was based on my experience of being involved with the PISTE clinical trial. This trial compared the use of mechanical thrombectomy (MT), plus standard care, compared with standard care alone, in the treatment of acute ischaemic stroke. This trial, along with other trials published around this period, found that the use of mechanical thrombectomy was associated with improved clinical outcomes at 90 days. I undertook a within-trial cost-effectiveness analysis of the PISTE clinical trial, using individual patient-level data. I then combined evidence from multiple clinical trials in a meta-analysis, and extrapolated beyond the trial period, to estimate the lifetime cost-effectiveness of mechanical thrombectomy.

However, subsequent discussion with the principal investigator (PI) on the PISTE trial identified several key challenges which were likely to present a barrier to the timely implementation of mechanical thrombectomy into routine clinical practice. These included, but were not limited to, the capital investment required to purchase the biplane angio suite necessary for mechanical thrombectomy and the configuration and cost of a dedicated workforce trained in the delivery of this procedure. Without considering the impact of these challenges within our economic evaluation, it was not possible to advise whether or not mechanical thrombectomy was likely to be cost-effective when implemented in routine clinical practice. To address this challenge, I worked alongside the PI of the PISTE trial to determine the budget impact and workforce configuration required to deliver thrombectomy in practice. We then scaled this up to the 27 comprehensive stroke centres required to treat the eligible population in the UK. To determine if, following the inclusion of these additional factors, the use of thrombectomy was still likely to be cost-effective in routine

practice, I conducted a Value of Implementation analysis. In addition to estimating the total value of perfect implementation, I estimated the breakeven level of thrombectomy required such that the benefit of implementation exceeded the cost.

My second case study was based on the CAVA clinical trial which compared the safety of three venous access devices for the delivery of long-term anti-cancer therapy: HICK, PICC and PORT. I initially undertook a cost-utility analysis alongside the CAVA trial. The study found that the cost of PORT was comparable with HICK (-£45) and greater than PICC (£1,665), but despite the significantly reduced rate of complication associated with a PORT, that there was no meaningful difference in QALYs between any device. However, a device-specific quality of life measure used within the CAVA study, alongside previous research, suggested a preference for PORT. Given the complex nature of implementing medical devices, where multiple outcomes may be relevant to multiple stakeholders, the cost-per-QALY metric may not have been sufficient for decision making. For this reason, I undertook a cost-consequence analysis to estimate a range of clinical and economic outcomes relevant to patients and decision-makers. However, several additional challenges remained with regards to implementation which were not captured within the CAVA trial.

The CAVA clinical trial was a pragmatic trial. As such, HICK, PICC and PORT were delivered according to current standard practice within the participating centre. This meant there was variation in how devices, particularly PORT, were delivered within the trial. This variation in practice fed through into heterogeneity in the cost of a PORT across centres. Discussions with clinicians highlighted that a nurse-led service would provide the most feasible and cost-effective route to deliver a PORT in routine clinical practice. For this reason, I worked alongside nurses and radiologists within oncology centres at The Beatson (Glasgow) and The Christie (Manchester) to develop a plausible implementation strategy, based on a nurse-led model, for the implementation of PORT. The Value of Implementation framework typically adopts

the QALY as the measure of benefit associated with a technology. However, due to the potential limitations of the QALY in this context, I used an estimate of the reduction in infection rate associated with PORT. I then used the Value of Implementation framework to answer questions relating to implementation which would be more useful to decision-makers. For example, given that HICK, PICC and PORT are likely to remain device options in clinical practice, what is the value of providing a PORT service to half of the eligible patient population? What is the minimum willingness to pay for infections avoided for the benefits of PORT to exceed the costs?

Results

The first review showed that there is a high level of variation in how implementation is considered within the evaluation of health technologies funded by the HTA programme in the UK. Methods for examining implementation ranged from single stakeholder engagement events to a more comprehensive process evaluation. There was no obvious trend in how the approach to implementation had evolved over the review period. Approximately 50% (22/42) of studies included an economic evaluation. Of these, two studies included the use of qualitative data obtained within the study to quantitatively inform aspects relating to implementation and economic evaluation in their study.

The second review identified 33 unique studies which included a methodology for combining implementation and economic evaluation. The methods identified could be categorised into four broad themes – i) policy cost-effectiveness approach, ii) Value of Information and Value of Implementation approach, iii) study design approach, and iv) costing of systems change approach. I identified a trend over time from methods which adopted the policy cost-effectiveness approach towards methods which considered the trade-off between the Value of Information and Value of Implementation. More recently, methods have been developed to inform study

design and to define, measure and cost individual components of the implementation process for use in economic evaluation.

Based on our review and content analysis of the methods available to incorporate implementation alongside economic evaluation, we developed a conceptual model to map out where these methods may be most relevant in the development, evaluation and implementation of a health technology.

My cost-utility analysis of mechanical thrombectomy, compared with standard care, showed that thrombectomy was highly cost-effective over a lifetime horizon, with an ICER of £3,466 per QALY gained. The expected value of perfect information per patient eligible for MT in the UK was estimated at £3,178. The expected Value of full Implementation of MT was estimated at £1.3 billion over five years. At an implementation level of 30% achieved throughout the UK healthcare system, I estimated that the population health benefits obtained from this treatment were greater than the cost of implementation.

This case study demonstrated the limitation of considering cost-effectiveness from the perspective of a lifetime cost-per-QALY metric in the context of a complex intervention. Without considering how this technology would be implemented within routine clinical practice, it would only have been possible to provide a partial view of the potential cost-effectiveness of mechanical thrombectomy.

Estimating the Value of Implementation, by incorporating additional costs required to implement this health technology in practice, alongside the eligible population expected to benefit from this technology, allowed us to provide decision-makers with a more realistic assessment of the cost-effectiveness of thrombectomy. The inclusion of such data is not common in the assessment of health technologies in a clinical setting. However, without these additional data, I would not have been able to

provide a realistic evaluation of the potential cost-effectiveness of thrombectomy in routine clinical practice.

It is important to note that many challenges relating to the implementation of thrombectomy were not addressed in my analysis. These challenges include the need to reconfigure the clinical pathway to minimise the time from stroke onset to treatment and the role of imaging and patient selection in the pathway. Other studies have addressed these issues and continue to feed into our understanding of the implementation of thrombectomy.

Therefore, a key lesson from this case study was that engagement with clinicians and other stakeholders involved in the delivery of this health technology was crucial to understanding and modelling its potential cost-effectiveness in routine clinical practice. This finding is likely to be relevant to researchers considering the potential cost-effectiveness of any complex intervention in a clinical setting. Early engagement with clinicians and stakeholders would allow us to better plan for the data requirements and research methods necessary to fully evaluate the cost-effectiveness of complex interventions in routine clinical practice.

Our cost-consequence analysis of the CAVA trial found that PORT was superior in terms of overall complication rate, compared with both HICK (0.422 (0.286 to 0.622)) and PICC (0.295 (0.189 to 0.458)) and less likely to lead to an unplanned device removal. There was no meaningful difference in the number of days of chemotherapy interruption or health utilities. Total cost with device in situ was lower on PORT, compared with HICK (£-98.86 (-189.20 to -8.53)) and comparable with PICC (-£48.57 (-164.99 to 67.86)).

The value to the NHS of full implementation (i.e., 100% of patients receiving a PORT), compared with HICK and PICC, respectively, is approximately £24m and £800,000.

That is, if we achieve full implementation, the monetary value we obtain from infections avoided, is greater than the cost of setting up a PORT service. If a PORT is received by 50% of eligible patients, the Value of Implementation of a PORT is approximately £12m compared with HICK, and £400,000 compared with PICC. Any level of implementation (greater than zero) of a PORT service is likely to be cost-effective, compared with both HICK and PICC. This is due to the value of the infections avoided, compared with the cost of implementation and per patient treatment cost. The implementation cost of a PORT service could be as high as £24m, compared with HICK, and £800,000 compared with PICC, and still be considered cost-effective. If a PORT is offered to 50% of patients requiring a VAD, the maximum cost of implementation for which PORT would still be considered cost-effective is £12m compared with HICK, and £400,000 compared with PICC. At a level of £0 willingness to pay for infections avoided, the value of implementation of a PORT service exceeds its cost, compared with HICK. The minimum level of WTP for a PORT to be considered cost-effective, compared with PICC, is £10,500.

Analytical methods, such as Value of Implementation analysis, can help us to estimate the cost-effectiveness of health technologies in routine practice. This will be particularly relevant in the context where the benefits of the technology can be captured within the QALY metric. This was likely to be true of thrombectomy, where the benefits of treatment are well characterised by length and quality of life.

In my second case study, I used infection rate as a measure of the benefit associated with PORT to undertake the Value of Implementation analysis. While the reduction in infection is a clear benefit of PORT, other factors, such as patient acceptability and cost represent additional domains of value which are relevant to patients and decision-makers. As such, other methods to identify and disaggregate the value of a PORT, such as multi-criteria decision analysis, may also have been relevant.

Using the Value of Implementation framework in this case study allowed me to answer additional questions relating to implementation which were relevant to decision-makers. However, qualitative research methods could have been employed earlier in this study to identify what patients value in the context of a venous access device and how best to capture and incorporate these data into an economic evaluation.

Conclusion

This thesis has made several unique contributions to the challenge of incorporating implementation within the economic evaluation of health technologies. My literature reviews have shown that many of the tools we need to consider implementation are already available. However, they are infrequently and inconsistently used in practice. I have described the purpose for which these methods were developed, how these methods differ from one another, and where gaps still remain. The conceptual model developed from my review of current methods suggested where in the HTA process these methods may be most applicable.

Both of my case studies highlighted the limitations of traditional methods for cost-effectiveness analysis, based on the cost-per-QALY approach, in the context of complex interventions. This is because complex interventions typically require us to consider how a technology will be implemented in routine clinical practice.

In my first case study, I worked closely with stroke clinicians and stakeholders to understand the challenges of implementing mechanical thrombectomy in routine practice. This allowed me to incorporate additional costs not captured within the trial setting, ensuring that my research was addressing questions relevant to stakeholders and decision-makers in this area. Furthermore, I showed that the QALY benefit to the eligible population from mechanical thrombectomy was likely to exceed the cost of implementation if we can achieve at least 30% implementation across the UK. This

additional evidence means that decision-makers were better able to plan for the resource requirements necessary to implement this technology in their own setting. It also demonstrated that it was not necessary to achieve full implementation to realise the benefits of mechanical thrombectomy.

In my second case study, I recognised that, in the context of a complex intervention, involving multiple outcomes and stakeholders, the applicability of the cost-per-QALY framework may have been limited in capturing the full value of a venous access device. For this reason, I undertook a cost-consequence analysis to evaluate a range of clinical and economic outcomes relevant to patients and decision-makers. This allowed patients and decision-makers to consider the importance they place on each of these outcomes when choosing an appropriate device. Recognising the heterogeneity in service delivery and cost within the CAVA trial, I worked alongside radiologists and nurses to develop a plausible scenario for the delivery of a PORT service in routine practice. I used the Value of Implementation framework to estimate the total expected Value of Implementation. I also then used this framework to answer additional questions related to implementation, such what is the value of delivering a PORT to just 50% of patients requiring a VAD? What is the minimum willingness to pay for infections avoided for the benefits of PORT to exceed the cost of implementation?

My case studies allowed me to demonstrate how current methods can be used to incorporate implementation within the economic evaluation of a health technology. They also allowed me to identify gaps in our current approach. For example, implementation is too often considered retrospectively, and on an ad hoc basis. Additional methods which explicitly incorporate implementation and economic evaluation alongside one another may be required. However, we already have sufficient methods to make progress in this area. What is missing is practical and

consistent guidance on where, when, and how available methods can be incorporated in the development, evaluation, and implementation of a health technology.

Both the Department for Health and Social Care and the NHS have identified the implementation of clinically effective and cost-effective health technologies as a key priority for the healthcare system. Therefore, the time is apt for funders, reimbursement agencies, decision-makers, and researchers to work together to develop guidance demonstrating how implementation can be incorporated within the economic evaluation of a health technology. Health research funders should consider whether implementation ought to play a greater role within the evaluation of complex interventions. Reimbursement agencies should consider if we need to develop formal process by which the issue of implementation can be considered alongside the more traditional mechanisms for assessing health technologies.

Contents

List of tables

List of figures

Abbreviations

ABM	Agent-based model
CAVA	Cancer And Venous Access (CAVA) clinical trial
CBA	Cost-benefit Analysis
CCA	Cost-consequence Analysis
CEA	Cost-effectiveness Analysis
CUA	Cost-utility Analysis
CI	Confidence Interval
DCE	Discrete Choice Experiment
DES	Discrete Event Simulation
HICK	Subcutaneously tunnelled central catheters
HTA	Health Technology Assessment
ICER	Incremental Cost-effectiveness Ratio
MRC	Medical Research Council
MCDA	Multi-criteria Decision Analysis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMB	Net Monetary Benefit
PICC	Peripheral inserted central catheters
PISTE	Pragmatic Ischaemic Stroke Thrombectomy Evaluation clinical trial
PORT	Implantable chest wall port
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted Life Year
RCT	Randomised Controlled Trial
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
UK	United Kingdom

VAD	Venous access device
VoI	Value of Information

Acknowledgements

I am extremely grateful to my supervisors Professor Olivia Wu and Dr Kathleen Boyd for their insightful feedback and guidance over the course of my PhD. Without their time and patience, and our many long conversions on implementation and economic evaluation, this PhD would not have been possible.

The genesis of this PhD was in my first conversations with principal investigator of the PISTE clinical trial Professor Keith Muir. I am extremely grateful to Keith for generously spending time explaining to me the issues regarding the implementation of mechanical thrombectomy. Without his passion for stroke care and patients, this PhD would not have been developed.

I would also like to thank my colleagues at HEHTA, particularly the residents of room 202, for their support, encouragement, and friendship over the last 8 years. Finally, I must express my gratitude to my mum, dad and brother for their unconditional support and belief in me.

A note on terminology

The overall theme of this thesis is on the topic of incorporating implementation within the economic evaluation of health technologies. When I discuss the importance of considering implementation, I refer to the overall benefit we can get from incorporating a range of implementation issues within our evaluations. This will often take the form of costs associated with implementation which are often not captured within the economic evaluation of health technologies. However, as discussed in this thesis, it may also relate to the limitations of the cost-per-QALY framework in the context of complex interventions where multiple outcomes are required to demonstrate value and encourage implementation. Distinct from this is a formal tool which is called "Value of Implementation", which was formalised by Walker et al. (2014) (1). This is a very specific tool which estimates the monetary value of health benefits associated with activities designed to increase the uptake of health technologies.

In Chapter 3, I review a range of methods which are available for considering implementation alongside economic evaluation. In this chapter, I define four distinct approaches (or classifications) of methods for incorporating implementation - i) policy cost-effectiveness approach, ii) Value of Information and Value of Implementation approach, iii) study design approach, and iv) costing of systems change approach. These classifications are my own, and another research may well classify the available methods differently. However, I felt that such classifications were necessary to bring structure to a literature which is at present disparate and difficult to navigate. The third and fourth classifications are largely self-explanatory, and relate to methods developed to either incorporate implementation issues into a study design, or methods which break down the process of costing systems changes. The first classification – "policy cost-effectiveness" – was coined by Mason et al. (2001) (2). Most commonly this refers to the economic evaluation of alternative implementation strategies (e.g., strategies to increase uptake, such as public awareness campaigns).

This contrasts with methods which seek to bring implementation issues (e.g., costs) into an economic evaluation. While the term policy cost-effectiveness may be somewhat ambiguous, it does refer to a distinct group of methods. For this reason, I choose to maintain this definition. Similarly, a group of methods are available which estimate the Value of Information (Claxton et al. (1999) (3)), Value of Implementation (Walker et al. (2014) (4)), or both simultaneously (Fenwick et al. (2008) (5)). While similar, these refer to three distinct methods. I have tried to make the distinctions I have highlighted here consistent throughout this thesis.

Author's declaration and contribution statements

Author's declaration

I declare that, except where explicit reference is made to the contribution of others, this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Robert Heggie

Contribution statements

Chapter 1: The drafting of chapter 1 was led by myself, with oversight and suggestions from my supervisors Olivia Wu and Kathleen Boyd.

Chapter 2: The conceptualisation of this review was led by myself and my supervisors Olivia Wu and Kathleen Boyd. The search, data extraction, analysis and manuscript drafting were undertaken by myself. The search was validated, and manuscript reviewed and edited, by my supervisors Olivia Wu and Kathleen Boyd.

Chapter 3: The conceptualisation of this review was led by myself and my supervisors Olivia Wu and Kathleen Boyd. The search, data extraction, analysis and manuscript drafting were undertaken by myself. The search was validated by Hanin Kamaruzaman. The manuscript was reviewed and edited by Hanin Kamaruzaman and my supervisors Olivia Wu and Kathleen Boyd.

Chapter 4: The conceptualisation and methodological design of this project was led by myself, my supervisor Olivia Wu, and Keith Muir. The analysis and manuscript drafting were undertaken by myself. All co-authors provided feedback and edits on the final manuscript.

Chapter 5: The conceptualisation and methodological design of this project was led by myself, my supervisors Olivia Wu and Kathleen Boyd, Nishant Jaiswal and Neil Hawkins. The analysis was undertaken by myself. Manuscript drafting was undertaken by myself. All co-authors provided feedback and edits on the final manuscript.

Chapter 6: The drafting of chapter 6 was led by myself, with oversight, suggestions and editing from my supervisors Olivia Wu and Kathleen Boyd.

Publications and other outputs

The following publications, conference presentations and panel discussions have resulted from the research described in this thesis.

Publications

Chapter 2 has been published as:

Heggie, R., Boyd, K. and Wu, O. (2021) How has implementation been incorporated in health technology assessments in the United Kingdom? A systematic rapid review. Health Research Policy and Systems, 19, 118. (doi: 10.1186/s12961-021-00766-2)

Chapter 3 has been prepared for submission as:

Heggie, R., Boyd, K., Kamaruzaman, H., Wu, O. (2023) What methods are currently available for incorporating implementation considerations within the economic evaluation of health technologies? A systematic review. Prepared for submission to Implementation Science

Chapter 4 has been published as:

Heggie, R., Wu, O. , White, P., Ford, G. A., Wardlaw, J., Brown, M. M., Clifton, A. and Muir, K. W. (2020) Mechanical thrombectomy in patients with acute ischemic stroke: a cost-effectiveness and value of implementation analysis. International Journal of Stroke, 15(8), pp. 881-898. (doi: 10.1177/1747493019879656) (PMID:31564243)

Chapter 5 is under review as:

Heggie, R., Jaiswal, N., McCartney, E., Moss, J., Menne, T., Jones, B., Boyd, K., Soulis, E., Hawkins, N., Wu, O. (2021) Central venous access devices for the delivery of systemic anticancer therapy: an economic evaluation. Under review in Value in Health

Conference presentations

Heggie, R., Wu, O. , White, P., Ford, G. A., Wardlaw, J., Brown, M. M., Clifton, A. and Muir, K. W. (2017) Mechanical Thrombectomy in Patients With Acute Ischemic Stroke: A Cost-Effectiveness and Value of Implementation Analysis. 3rd European Stroke Organisation Conference (ESOC), Prague, Czech Republic, 16th-18th May 2017

Heggie, R., Boyd, K. and Wu, O. (2019) Should health economists care about implementation? School of Health and Wellbeing Research Away Day. Glasgow, United Kingdom. 26th February 2019

Heggie, R., Boyd, K. and Wu, O. (2021) Should health economists care about implementation? The Health Economists' Study Group Summer 2019 Meeting. Norwich, United Kingdom. 3rd-5th July 2019

Heggie, R., Boyd, K. and Wu, O. (2021) Should health economists care about implementation? European Health Economics Study Group (EuHEA). Porto, Portugal. 4th-6th September 2019

Heggie, R., Boyd, K. and Wu, O. (2021) Incorporating implementation within the economic evaluation of health technologies. School of Health and Wellbeing Postgraduate Seminar Series. Glasgow, United Kingdom. 8th December 2021

Heggie, R., Jaiswal, N., McCartney, E., Moss, J., Menne, T., Jones, B., Boyd, K., Soulis, E., Hawkins, N., Wu, O. (2021) Central venous access devices for the delivery of systemic anticancer therapy: an economic evaluation. European Health Economics Study Group (EuHEA). Oslo, Norway. 5th-8th July 2022.

Panel discussion

Heggie, R., Hoomans, T., Clarke, C., Walker, S., Clifton, E. (2022) A Lifecycle Approach to HTA: The Role of Implementation Alongside Economic Evaluation. Health Technology Assessment International (HTAi). Utrecht, The Netherlands. 25th - 29th June 2022

COVID-19 impact statement

The beginning of the COVID-19 pandemic occurred approximately mid-way through my PhD and the University's move to home-based working occurred shortly before our deadline for the NIHR HTA monograph for the CAVA clinical trial. This presented some challenges for the completion of this project. Firstly, the analysis involved working with many datasets. While working in the office, I was able to work with three screens (laptop plus two PC monitors). This enabled me to have multiple screens opened at the same time and made understanding and analysing the data much more efficient. When I move to home working - laptop only – I was still able to work, but my work was much less productive than previously. In addition, it made it more difficult to speak to project partners and colleagues about the work we were doing and any problems we were encountering. Taken together, the move to home working meant that, while I was still able to work, my work was less productive, and the completion of the CAVA project took longer than planned.

Chapter 1: Introduction

1.1 Background

1.1.1 Implementing evidence-based medicine

Evidence-based medicine is designed to ensure that patients receive access to health technologies which have been shown to be safe and clinically effective. Research studies, such as randomised controlled trials and observational studies, can provide such evidence. On the basis of this evidence, health technology assessment agencies, such as the National Institute for Health and Care Excellence (NICE), can evaluate the clinical- and cost-effectiveness of these technologies, and make recommendations for use in the National Health Service (NHS) in the UK. However, for any health technology to bring benefit to patients, it must be implemented in a timely, effective, and cost-effective manner. In 2005, the Audit Commission found that only 25% of NHS bodies could verify that NICE technology appraisals had been implemented within three months of publication (6). Several studies have estimated an average lag of approximately 17 years from research findings to clinical practice (7-11), with one study finding that only about half of evidence-based practices ever reach widespread use in clinical practice (12). While the accuracy and usefulness of any specific estimate is disputed (13) and likely to vary by time and setting, it is widely accepted that implementation is often slow and sub-optimal. A review of attitudes towards evidence-based medicine internationally found that, among doctors and nurses surveyed, about only half considered their clinical practice to be evidence-based (14). Both the Department for Health and Social Care and the NHS have identified the implementation of clinically effective and cost-effective health technologies as a key priority for the healthcare system (15, 16).

There are many challenges associated with implementing a health technology in practice, including the volume and applicability of clinical guidelines, competing priorities among local and national decision-makers, and perhaps most commonly,

resource constraints (17). There is also often a gap between what is studied in clinical research and what clinicians actually do (18). For all these reasons, the publication of research evidence is often insufficient to change clinical practice (19). The challenges associated with implementation are compounded in the context of complex interventions. While no clear distinction can be made between a "simple" and a "complex" intervention, a complex intervention is typically defined as one which involves several interaction components, outcomes and stakeholders (20).

Implementation can broadly be defined as the process of executing a plan designed to bring about change. Implementation science is, by its nature, a highly multidisciplinary field, involving a range of skills from economics and management science to sociology and psychology. The tools of implementation science have applications in many areas ranging from management science to healthcare. Indeed, there are over 100 tools available for practitioners in the academic literature on implementation science (21).

Skolarus et al. (2017) undertook a systematic review of frameworks published in the field of implementation and diffusion (22). They sought to evaluate the role of each framework and the impact of each approach on the field of implementation science, based on the number of citations it received. In 2006, Graham et al. published "Lost in Knowledge Translation: Time for a Map?" (23). According to Skolarus et al. (2017), this is the most highly cited paper in the field of implementation. To bridge what the authors call the "knowledge-to-action" (KTA) gap, the authors developed a conceptual framework based on the key elements they believe are crucial to successful implementation of new research. The authors take the perspective that the process of implementation can be split into two stages: i) knowledge creation, and ii) action cycle. The first stage may consist of generating knowledge via the use of systematic review and meta-analysis. The second stage involves identifying a specific problem in current practice to address and adapting the tool based on feedback from stakeholders regarding the context and potential barriers to implementation.

In 2004, the UK Department of Health commissioned Greenhalgh et al. to undertake an extensive systematic review of the literature on the implementation (or diffusion) of service innovations, particularly in the area of health care research (24). According to Skolarus et al. (2017), this is the second most highly cited paper in the field of implementation. The authors undertook a "meta-narrative" review which sought to map out the history and development of implementation and diffusion theory from alternative research traditions (e.g., rural sociology, health promotion, evidence-based medicine). Their final product is a unifying conceptual model which synthesises all of the key components and process identified in the literature as being relevant to the implementation and diffusion of health service research findings.

Damschroder et al. (2009) recognised that there were a surplus of terminologies and concepts used to explain the implementation process, in addition to an overlap and repetition of theoretical frameworks developed from them (25). In response to this, Damschroder et al. (2009) developed the "Consolidated Framework for Implementation Research (CFIR)" which outlined a nomenclature for navigating the field of implementation science. The CFIR is composed of five major domains: intervention characteristics (e.g., adaptability and complexity), outer setting (e.g., patients and resources), inner setting (e.g., culture and leadership), characteristics of the individuals involved (e.g., enthusiasm and self-efficacy), and the process of implementation (e.g., plan and evaluate).

Beyond simply defining and categorising "constructs" (specific barriers to implementation), the CFIR aims to equip implementation researchers with a framework which allows them to select constructs to use in the identification, evaluation and explanation of the implementation process. However, the authors stress that while the CFIR identifies a list of constructs which are believed to influence the implementation process, the CFIR does not specify the interaction between these constructs. Instead, the CFIR provides a framework by which researchers can

hypothesise and empirically test interactions and relationships between constructs. Prior to beginning a process of implementation, an assessment is undertaken to identify potential barriers to implementation. The CFIR is designed to offer a framework by which researchers can identify these barriers and develop a mechanism for collecting the required data to monitor implementation.

The RE-AIM framework was designed over two decades ago and is another of the most commonly cited tools in implementation science (26). It was designed to evaluate the impact of public health interventions at the individual, clinical, organisational and community level, in terms of reach, efficacy, adoption, implementation and maintenance. An update of the framework in 2019, based on user feedback, places increased emphasis on cost, benefit, the challenge of implementation, and the use of qualitative methods to understand what works and why (27).

Implementation frameworks can either be used prospectively or retrospectively. The RE-AIM framework is designed to be used to plan and evaluate implementation, whereas the CFIR is particularly suited to understanding why an intervention was either successful or resulted in failure (28).

Both the Greenhalgh (2004) and Damschroder (2009) frameworks explicitly state that the purpose of their model is to serve as a "starting point" and memory aid for understanding the process of implementation and should not be seen as a formula which provides a causal relationship between all components involved in implementation. It is notable that three of the most highly cited papers in the field of implementation all attempt to do the same thing; define a consistent terminology for the concepts necessary to understand implementation and to bring these concepts together into a conceptual model which can be used to understand the process of implementation. This perhaps speaks to a lack of consensus in the field and the

difficultly in identifying a one-size-fits-all approach to implementation. It may never be possible to provide an implementation framework which is able to define clear causal pathways between all inputs and outputs in a complex organisation, process or context. However, is it perhaps the key weakness of the current methods available that they typically consist of frameworks or conceptual models which highlight key issues to consider in implementation, rather than a step-by-step approach for "solving" the implementation problem. Nevertheless, researchers working in implementation science continue to strive to make their discipline more transparent and accessible to those in other fields interested in applying these methods (29).

1.1.2 Implementation within economic evaluation

Given the breadth of frameworks and academic traditions from which implementation science has developed, it is necessary to explain the challenge of incorporating implementation within the context of evaluating health technologies. In the field of healthcare, implementation science has been defined as "*the scientific study of methods to promote the systematic uptake of research findings and other EBPs (evidence-based practices) into routine practice, and, hence, to improve the quality and effectiveness of health services* (12)."

The need to consider implementation has been recognised by funders and reimbursement agencies alike (30, 31). The Medical Research Council (MRC) is one of the leading organisations responsible for co-coordinating and funding medical research in the UK. In 2021 the MRC updated their guidance for developing and evaluating complex interventions. They recommend four key phases in this process: identifying or developing an intervention, assessing feasibility, evaluation, and implementation. At each key phase in the process, economic evaluation should be considered. Importantly, this is not a linear process. It is a cyclical process which can begin and return to any phase as appropriate. However, the MRC guidance on how economic evaluation can contribute to the process is limited to suggesting that a

broader range of techniques (e.g., cost-consequence, cost-benefit) may be more suited to capturing multiple outcomes from a multi-stakeholder perspective. No new methodological approaches are suggested. In particular, there is no specific guidance as to how economic evaluation and implementation should be considered alongside one another.

A summary of the key differences between an economic evaluation of a health technology and an economic evaluation of implementation is given in the table below (Table 1), adapted from Eisman et al. (2000) (32).

Table 1: Characteristics of economic evaluations for interventions versus implementation.

Characteristic	Economic evaluation of interventions	Economic evaluation of implementation
Relevant costs	Discrete cost of intervention	Expansive cost of intervention plus implementation strategy
Relevant benefits	Clinical outcomes	Implementation, service, clinical outcomes
Time horizon	Variable, from less than one year to lifetime	Often multi-year, can include short term implementation and long-term sustainment
Perspective	Variable, from societal to health care system	Variable, from societal and health care system, but also local budget holders
Study design	Research methods often chosen to maximise internal validity and methodological rigor	Focused on external validity, pragmatism, feasibility for practice settings
Impact on context	Low. Often standardised interventions delivered in ideal settings	High. Adapted to context, with variability in intervention, implementation across settings.
Relevant decision-maker	Healthcare payers, reimbursement agencies	Local or national budget holders

Adapted from Eisman et al. (2000).

In the UK, NICE provide guidance to the National Health Service (NHS) on the cost-effectiveness of health technologies (33). The NICE guidance for technology appraisal sets out the methodological approach required for a comparative cost-effectiveness evaluation of a health technology for reimbursement purposes. This is typically based on a cost-utility approach, where the incremental cost of a health technology is compared with the incremental utility (e.g., quality-adjusted life year) gained. If the ratio of cost to utility is less than a given willingness-to-pay threshold (typically £20,000-30,000 in the UK), the technology is regarded as representing a cost-effective use of resources.

Under this framework, economic evaluation has typically focused on the cost of providing a health technology at a "per patient" level, rather than as a full package of costs associated with implementing, delivering and sustaining a health technology. However, an update to the NICE guidance for technology appraisal in 2022 placed increased emphasis on additional costs associated with implementation, stating that an evaluation should include the full additional costs associated with introducing a technology (33). This includes costs relating to infrastructure and training. The new guidance also states that we should consider potential rates of uptake and resources constraints, and the impact that this may have on our assessment of a health technology.

The growth in the use of medical devices, diagnostics, and more complex clinical pathways in healthcare means that it is becoming increasingly necessary to consider the challenges of complex interventions in a clinical setting. To evaluate the clinical- and cost-effectiveness of these technologies, it is necessary to consider how they will be implemented, how they will be used in practice, the range of stakeholders involved, and which clinical or economic outcomes may be relevant.

Complex interventions have typically been the reserve of public health research.

This is because public health interventions may impact on a range of outcomes, such as health, education and the justice system. Local government is largely responsible for the implementation of public health interventions. In addition to health, local government also has a responsibility to consider the wider welfare of individuals within the community. The NICE guidance on the evaluation of public health interventions highlights the limitations of the cost-per-QALY approach in the context of public health interventions, suggesting that a narrow focus on health benefits alone may not be suitable from a public health perspective (34). Despite this, the cost-per-QALY approach continues to play an important role in public health research, as it allows for a comparison of the value of interventions across disease areas or programmes. However, NICE public health guidance also encourages the use of techniques such as cost-benefit and cost-consequence analysis to capture a broader range of costs and outcomes relevant from a public health perspective.

The methodological techniques required to evaluate health technologies were developed by the research community. However, the scope of what should be included within a health technology assessment for the purpose of reimbursement in the UK is largely driven by bodies such as NICE. Given this, the lack of remit on behalf of NICE to formally evaluate implementation may help to explain the lack of methodological guidance in this area (35).

1.1.3 Economic evaluation of implementation strategies

The cost of implementing a health technology has real consequences for population health, in terms of the opportunity cost of the resources required to bring about change. Therefore, in addition to including implementation costs within our analyses, it is crucial that we also assess the costs and consequence of alternative implementation strategies tdesigned to increase the uptake of health technologies. While economic evaluation has come to play a key role in health technology assessment, its use within implementation research is limited (36). A systematic

review in 2004 concluded that there was no robust and generalisable evidence base upon which to determine the costs and benefits of guidelines dissemination or alternative implementation strategies (37). This was largely due to the poor analytical methods used to compare strategies. Furthermore, recommendations offered in clinical guidelines did not typically include economic considerations. A subsequent review in 2007 found that, while the use of economic evaluation methods to inform guideline implementation had increased, poor reporting and a lack of methodological rigour meant that evidence on the costs and benefits of alterative guideline implementation strategies was still not sufficient for decision making (38).

Another recent review examined the use of economic evaluation methods in implementation studies (39). They found that while the standard of these evaluations was typically high, the use of economic evaluation in implementation studies was uncommon. In addition, the methods used were the standard methods of economic evaluation (e.g., cost-effectiveness, cost-utility, cost-consequence, and cost-benefit), highlighting a lack of specific methods for combining implementation and economic evaluation.

The appearance is of two disciples, economic evaluation and implementation science, which sit parallel to one another and do not routinely interact. Indeed, Eisman et al. (2020) highlight that, despite the growth of implementation science over the past two decades, the use of economic evaluation in implementation studies is uncommon - less than 10% of implementation studies incorporated the cost of implementation (32) and even less considered relative cost-effectiveness of competing implementation strategies (40).

While there is little clear guidance from funders and reimbursement agencies on how to consider the challenge of implementation alongside the economic evaluation of health technologies, researchers have made steps in addressing this challenge.

Methods have been developed to facilitate the economic evaluation of implementation strategies (2), to incorporate implementation issues in study design (41, 42), to identify and measure the cost of each stage of implementation (17), and to consider the trade-off between the value of further information or further implementation (5). Despite this, the use of these methods is not common in practice.

1.2 Research motivation and origin

In 2016 I began work on the economic evaluation of the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised clinical trial (43). The trial compared the use of mechanical thrombectomy, plus standard of care, compared with standard of care alone for the treatment of acute ischaemic stroke. I applied the standard approach for economic evaluation alongside a clinical trial, following by a lifetime extrapolation, based on the methodology recommended by the National Institute for Health and Care Excellence Guide for Technology Appraisal (33). Following discussions with the principal investigator of the PISTE trial, it became clear that there were many issues which were likely to present a challenge for the implementation of mechanical thrombectomy in routine clinical practice. I realised that, despite following recommended practice for the economic evaluation of mechanical thrombectomy, I was still not really in a position to recommend whether or not this procedure would be cost-effective when delivered in a real-world setting.

I decided to review the literature to see how other researchers had approached the challenge of incorporating implementation within the economic evaluation of a health technology. I found that this was an area of active research, and that many methods were available to assist in this task. However, this landscape had not been well mapped out. The literature contained methods from a range of disciplines - from economic evaluation to business and management science - and from different analytical perspectives - qualitative and quantitative. However, there was little formal

guidance on how these methods should be applied in the evaluation of a health technology.

While implementation is not routinely considered within the assessment of a health technology, I believe that it should be. Any health intervention is only as good as its implementation. Therefore, implementation should not be a niche area of applied health research. For this reason, I chose to devote my PhD to building a body of work designed to map-out the methodologies which are currently available in this area and to demonstrate the value of using these methods to enrich our economic evaluation of health technologies and make our evaluations more useful to decision-makers.

Aim

The aim of this thesis is to demonstrate the value of considering implementation within the economic evaluation of health technologies.

1.3 Objectives of the thesis

1. Undertake a rapid systematic review of how implementation has been incorporated within the NIHR HTA programme in the UK.
2. Undertake a systematic review to identify and describe which methods are currently available for incorporating implementation considerations within the economic evaluation of health technologies.
3. Demonstrate how the Value of Implementation framework can be utilised to provide more useful evidence for decision-makers using two case studies.
    3.1. In the context of mechanical thrombectomy for acute stroke in the UK.
    3.2 In the context of venous access devices for the delivery of anti-cancer therapy in the UK.

1.4 Structure of the thesis

I have chosen to present my PhD using the "thesis by alternative format", offered by the University of Glasgow (2020). Since 2014 I have worked as a researcher within the Health Economics and Health Technology Assessment (HEHTA) group, within the School of Health and Wellbeing, University of Glasgow. I chose to present my PhD in this format as it allowed me to efficiently combine my role as a researcher within HEHTA with my role as a PhD student, by including as thesis chapters my published (or submitted) journal articles.

My PhD thesis is structured as follows.

Chapter 1 provided an introduction to my thesis. I began by providing some background to the issue of implementation alongside economic evaluation. I then explained how and why I decided to build my PhD on this topic. I finished this chapter by specifying the objectives of my thesis.

Chapter 2 is comprised of a published systematic review which seeks to determine how implementation has hitherto been considered alongside economic evaluation in studies funded by the National Institute for Health and Care Research's (NIHR) Health Technology Assessment (HTA) programme in the UK.

Chapter 3 is comprised of a systematic review which has been prepared for publication. This review aims to map out all the available methods for incorporating implementation alongside economic evaluation. While Chapter 2 was focused on how implementation has been incorporated within economic evaluation in practice, this review sought to determine the full range of methods which are available to researchers.

Chapter 4 is a case study and is comprised of a published research article which involves an economic evaluation of the use of mechanical thrombectomy, compared with standard of care, for the treatment of patients with acute ischaemic stroke. The evaluation involves a cost-effectiveness analysis of the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) clinical trial, a meta-analysis of seven similar trials involving mechanical thrombectomy, a cost-effectiveness model over a lifetime horizon, and a Value of Information and Value of Implementation analysis.

Chapter 5 is a case study and is comprised of a research article which has been submitted for publication. In this study, I undertook an economic evaluation of the use of three venous access devices - HICK, PICC and PORT - for the delivery of long-term anti-cancer therapy. I used a cost-consequence analysis to disaggregate a range of clinical and cost outcomes associated with the use of each device. I then use the Value of Implementation framework to provide guidance on the potential cost-effectiveness of a PORT service in routine clinical practice.

In Chapter 6 I provide a discussion and conclusion of my thesis. I present and interpret the results of my reviews and case studies and explain how they have addressed the objectives of this PhD. I also identify the main strengths and weaknesses of my analyses. I then provide my own reflection on the implementation process for the health technologies used in my case studies in the UK to date. Finally, I suggest areas for further research and explain the policy implications of my findings.

Chapters which are comprised of published or submitted journal articles are presented as published within their respective journals. Supplementary material, where included in the published or submitted article, is presented at the end of each chapter. Table and figure numbers have been revised to align with the structure of this thesis.

Chapter 2: How has implementation been incorporated in health technology assessments in the United Kingdom? A systematic rapid review

2.1 Foreword

Based on my experience from working on the PISTE clinical trial (43), it was clear to me that a meaningful and useful evaluation of the cost-effectiveness of some health technologies was only possible if we consider implementation. However, myself and my supervisors were not aware of any formal guidance which explains how implementation should be incorporated within an economic evaluation of a health technology. For this reason, I sought to determine what is currently happening in practice. I conducted a rapid systematic review of all studies published in the preceding six years by the NIHR's HTA programme which included the term "implementation" within the title or abstract. I chose a rapid systematic review as an efficient and pragmatic means to understand the current landscape regarding implementation and economic evaluation of health technologies. I chose the NIHR's HTA programme because it is the largest funder of applied health research in the UK, and as such, plays an influential role in how health technologies are assessed in the UK.

2.2 Title, authorship, and publication details

Heggie, R., Boyd, K. and Wu, O. (2021) How has implementation been incorporated in health technology assessments in the United Kingdom? A systematic rapid review. Health Research Policy and Systems, 19, 118. (doi: 10.1186/s12961-021-00766-2)

The overall work has been led by me and I take full responsibility for it. In this chapter, I use the terms 'we' and 'our' to recognise the contribution of all authors.

How has implementation been incorporated in health technology assessments in the UK? A systematic rapid review

Mr. Robert Heggie[1], Dr. Kathleen Boyd [1], Professor Olivia Wu[1]

[1] Health Economics and Health Technology Assessment (HEHTA), Institute of Health and Wellbeing, University of Glasgow, UK.

Robert.heggie@glasgow.ac.uk, Kathleen.boyd@glagow.ac.uk, Olivia.wu@glasgow.ac.uk

Corresponding author: Robert Heggie, Health Economics and Health Technology Assessment (HEHTA), Institute of Health & Wellbeing, University of Glasgow, 1 Lilybank Gardens, Glasgow G12 8RZ. Telephone: 0141 330 3047. Robert.Heggie@glasgow.ac.uk.

Keywords: implementation, economic evaluation, mixed methods, health technology assessment

2.3 Abstract

Objectives

Health interventions in a clinical setting may be complex. This is particularly true of clinical interventions which require systems reorganisation, behavioural change and/or when implementation involves additional challenges not captured within a clinical trial setting. Medical Research Council guidance on complex interventions highlights the need to consider economic evaluation alongside implementation. However, the extent to which this guidance has been adhered to, and how, is unclear. The failure to incorporate implementation within the evaluation of an intervention may hinder the translation of research findings into routine practice. This will have consequences for patient care. This study examined the methods used to address implementation within health research conducted through funding from the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme.

Methods

We conducted a rapid review, using a systematic approach. We included all NIHR HTA monographs which contained the word "implementation" within the title or abstract published between 2014 and 2020. We assessed the studies according to existing recommendations for specifying and reporting implementation approaches in research. Additional themes which were not included in the recommendation, but were of particular relevance to our research question, were also identified and summarised in a narrative synthesis.

Results

The extent to which implementation was formally incorporated, and defined, varied among studies. Methods for examining implementation ranged from single stakeholder engagement events to the more comprehensive process evaluation. There was no obvious pattern as to whether approaches to implementation had

evolved over recent years. Approximately 50% (22/42) of studies included an economic evaluation. Of these, two studies included the use of qualitative data obtained within the study to quantitatively inform aspects relating to implementation and economic evaluation in their study.

Discussion

A variety of approaches were identified for incorporating implementation within an HTA. However, they did not go far enough in terms of incorporating implementation into the actual design and evaluation. To ensure the implementation of clinical- and cost-effective interventions, we propose that further guidance on how to incorporate implementation within complex interventions is required. Incorporating implementation into economic evaluation provides a step in this direction.

Contribution to the literature

Current guidance on developing and evaluating complex interventions recommend that implementation should be considered as part of a cyclical process - development, feasibility/piloting, evaluation and implementation.

However, there are no formal guidelines or frameworks for how implementation can be incorporated within a holistic evaluation of a health technology.

Our review sought to identify if, and how, implementation has been taken into account in NIHR HTA research over the last six years.

Our review found that, although informal and inconsistent, methods are available to address implementation. Economic evaluation provides a set of tools which can aid implementation. However, further research and formal guidance is require to ensure the translation of research findings into clinical practice.

2.4 Background

Clinical research findings are often challenging to implement into routine clinical practice. This is particularly true of complex interventions which require significant system reorganisation, behavioural change or when implementation involves additional challenges which are not captured within a clinical trial setting. To ensure potentially beneficial research findings are effectively translated into routine clinical practice, you need to consider implementation.

There are many reasons why a potentially promising health technology observed in a clinical trial setting may not translate into an improvement in patient outcomes in a routine clinical setting (36). Among these, are the consideration of the barriers presented by costs and consequences not observed in a trial setting. The underuse of potentially beneficially health interventions has consequences in terms of potential patient benefit forgone (44).

Given that limited resources are available to generate population health outcomes, it is necessary to consider both the clinical- and cost-effectiveness of health technologies. This includes the choice of how, and indeed whether, to implement a health technology (32, 39). Economic evaluation provides a tool by which researchers can determine not only whether or not a health technology should be implemented and the extent of implementation required, but also the conditions under which a technology would be expected to be cost-effective. In the realm of complex interventions, it may also necessary to consider the cost-effectiveness of systems-level changes in health care provision and the cost-effectiveness of a single technology given alternative configurations of the healthcare system or clinical pathway.

Economic evaluation plays an increasingly crucial role in the evaluation of health technologies. However, despite this, economic evaluation rarely considers explicitly

the challenge of implementation. In recent years, some methodological tools have been developed which seek to bridge the gap between economic evaluation and implementation science (4, 5, 45, 46). Economic evaluation can potentially aid implementation in two ways. It can either be used to compare alternative implementation strategies – i.e. by considering the costs and consequences of implementation strategy X, compare with Y (45). Alternatively, implementation challenges can be incorporated within the economic evaluation of a technology – i.e. by adopting a mixed methods approach to economic evaluation (46).

Although typically the reserve of population health studies, complex interventions are increasingly relevant to interventions in a clinical setting. The line which distinguishes a "simple" from a "complex" intervention is blurred. Indeed, some argue that the distinction relates to your choice of research question, rather than the intervention itself (47, 48). From the perspective of a health technology assessment (HTA) body, whose remit is to consider the clinical-and cost-effectiveness of a health intervention, alongside equity and other social concerns, it could be argued that all interventions should be evaluated as complex interventions.

The importance of implementation is recognised in current Medical Research Council (MRC) guidance which highlights four phases for the assessment of complex interventions in a "cyclical sequence": development, feasibility/piloting, evaluation and implementation (49). Furthermore, as part of the implementation element of a complex intervention, the MRC guidance highlights dissemination, surveillance and monitoring, and long-term follow-up as the key issues to consider – all following the evaluation process. There is no discussion of how implementation can be used to inform the evaluation process. The MRC guideline update is currently underway and will address additional elements including early economic evaluation alongside the consideration of implementation (50).

The National Institute for Health and Care Research (NIHR) is the largest funder of health-related research in the UK. The need to undertake an economic evaluation of a health technology is a core component of the NIHR Health Technology Assessment (HTA) programme. Therefore, this rapid review sought to examine how implementation has been incorporated into NIHR HTA research over the recent six years.

2.5 Methods

We conducted a rapid review, using a systematic approach (51), to examine how implementation had being taken into account within NIHR HTA research. We applied the Proctor et al. (2012) checklist to identify how issues relating to implementation had been included within each study (52, 53). In addition, we identified additional themes that are relevant but not captured within the Proctor et al. (2012) checklist. A narrative synthesis was undertaken using these key themes to evaluate and discuss the identified studies.

Criteria for inclusion of studies

We included NIHR HTA monographs published over the period September 2014 - September 2020. All monographs which contained the word "implementation" within the title or abstract were included for review. Details of the search terms are given in Table 2. All monographs obtained from the search were included in the review. No exclusions were made based on participants, interventions, comparisons, outcomes, or study design. As the purpose of this review was to evaluate how implementation had been incorporated into all studies identified in the review, no quality assessment of the identified studies was required.

Table 2: Search terms used in literature review

#	Search terms	Results
1	health technology assessment winchester england.jn.	

2	implementation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	171,395
3	limit 2 to (abstracts and yr="2014 -Current")	65,022
4	1 and 3	42

Database searched

We searched the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) database via Medline.

Data extraction

All monographs were retrieved from Medline and exported to Endnote X7.0.2. They were initially reviewed and data were extracted by one researcher. For the purpose of validation, a random sample of 10 per cent of the monographs were subsequently reviewed independently by two additional researchers.

Data synthesis and presentation

All monographs were reviewed and assessed according to the Procter et al. (2012) checklist. This checklist was designed to provide guidance for researchers planning an implementation study. It contains a list of criteria which the authors recommend should be addressed within a study which aims to evaluate implementation. It is based on a review of successful implementation study research grants and the broader literature on implementation studies. Others checklists have been used when assessing the quality of studies used to inform implementation (54, 55). However, the focus of these checklists was on the quality of survey methods used to inform implementation, rather than a focus on how implementation had been incorporated into the study. To date, we are not aware of any commonly accepted tool for incorporating implementation into the development and evaluation of a study. For this reason, we believed the Proctor et al. (2012) checklist served as a suitable tool for

assessing the extent to which implementation issues have been incorporated within the studies included in our review. The key components relating to implementation that we used to critique the studies in our review, based on the Proctor et al. (2012) checklist, are identified in Table 3.

Since the Proctor et al. (2012) checklist was not designed for the purpose it was used in this study, a narrative synthesis was used to identify additional themes relevant to the issue of implementation, but not captured within the Proctor checklist (56, 57). We grouped "themes" not captured within Proctor. These themes were identified by the three study authors as themes which can aid the incorporation of implementation within economic evaluation. We identified and presented these themes alongside each study in matrix form in Table 4. As there was no "standardised metric" among studies, meta-analysis of results was not appropriate. We evaluated how the inclusion or exclusion of these additional themes served to hinder or facilitate the incorporation of implementation within the studies. We discussed heterogeneity of our results in terms of the consistency of approach and any pattern of change over time. Limitation to our review, such as databases searched and theme identified are, are discussed in the Discussion section.

2.6 Results

Four hundred and forty-five studies were identified in the NIHR HTA programme between September 2014 and September 2020. Forty-two (9%) of these studies included the word "implementation" in the title or abstract (Figure 1).

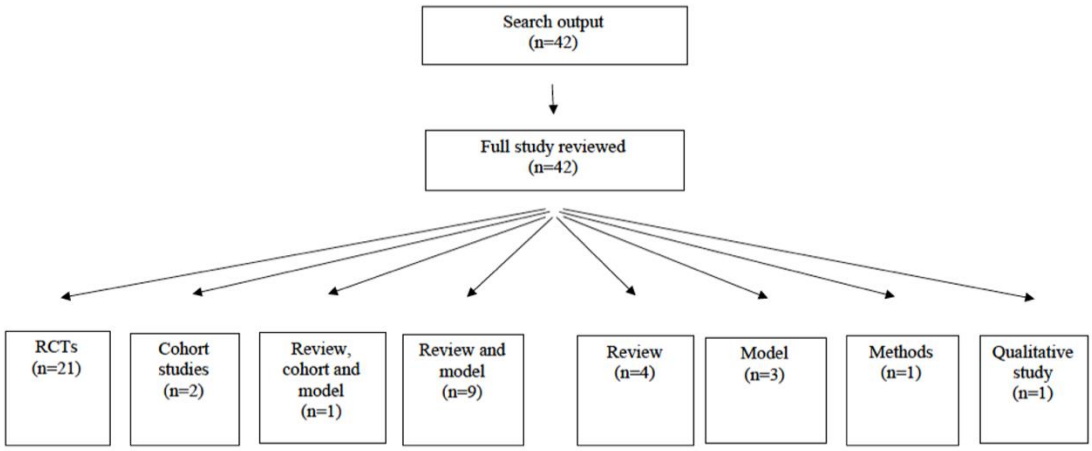


Figure 1: Types of studies identified in the review

The extent to which implementation was formally incorporated in the analysis, and how implementation was defined, varied among studies. No studies were excluded from the review. Seven themes which are not included in the Proctor et al. (2012) checklist (study type, process evaluation ("the process of understanding the functioning of an intervention, by examining implementation, mechanisms of impact, and contextual factors" (20)), barriers and facilitators, quantitative evaluation of implementation, economic evaluation, recommendations, and future work) were of particular relevance to our research question (Table 4).

Study type and setting

Twenty-one (50%) studies were either based on randomised controlled trials (RCTs) or pilot RCTs, while the remaining 50% of studies were a mix of cohort studies, modelling studies, or literature reviews (one monograph was a methods study) (Table 4). Twenty-eight studies assessed an intervention which applied to a clinical setting, while the remaining studies involved a population intervention (Table 4). Ten of the studies included discussed "setting" and the extent to which there was a readiness to adopt a new intervention or capacity to change (Table 3).

Process evaluation, stakeholder engagement and barriers and facilitators

A full process evaluation was included within fifteen of the studies (Table 4). Two studies included a conceptual model of the decision problem (58, 59) (Table 4). In evaluating an intervention aimed at reducing bullying and aggression in schools, Bonnell et al (58) used conceptual model to map out and disaggregate the relationships between intervention inputs and how these were mediated via behavioural change and environmental change to produce health outcomes. A justification for the choice of interventions being considered was given in every monograph reviewed (Table 3).

Twenty-nine of the studies included reported engaging with stakeholders during their study (Table 3). Thirty-four studies included a discussion on barriers and facilitators to implementing an intervention (Table 4). This was the most common method by which implementation was considered within the studies included in this review.

Quantitative evaluation of implementation and economic evaluation

Twenty-three of the studies included an economic evaluation (Table 4). Three studies included the use of quantitative data from a process evaluation to address implementation within their economic evaluation (60-62) (Table 4). For example, Richards (2018) used semi-structured interview to elicit data on nurse time required to undertake psychological care alongside cardiac rehabilitation in a pilot RCT. These data were then used to estimate the cost of nurse time.

Francis et al. (2020) undertook a multicentre RCT in 86 GP practices to evaluate the use of point of care testing to guide the management of antibiotic prescriptions in patients with chronic obstructive pulmonary disease (61). Embedded within the trial, a process evaluation found that staff time and initial training and equipment costs were a potential barrier to implementation of testing in routine practice. These findings were included within the economic evaluation. The results of the economic

evaluation were then presented in terms of cost-effectiveness (cost required to reduce the number of people consuming at least one dose of antibiotics by 1%), cost-utility (cost-per-QALY), and cost consequence (where costs were presented alongside clinical outcomes in tabular form, as to allow decision-makers to determine for themselves the value they place on each clinical outcome in the trial).

Seguin et al. (2018) undertook a mixed-methods study to evaluate the use of self-sample kits for increasing HIV testing among black Africans in the UK (60). The qualitative information collected in the process evaluation was used to guide the base case economic evaluation and to inform where sensitivity analyses were required around their assumptions. For example, the qualitative evaluation highlighted challenges in estimating the time required for a nurse to explain the intervention to the patient, since the majority of the appointment was spent explaining the study, obtaining consent and recording baseline characteristics. As a result, reliable data on the time required to explain how to use the self-sample kit was not obtained. This informed the sensitivity analysis of the cost-effectiveness results, where nurse time and cost required to explain the intervention were varied and demonstrated that this was highly unlikely to impact on the overall cost-effectiveness results.

In all three of these studies, this involved the inclusion of additional implementation-related costs of delivering an intervention. No studies evaluated the relative cost-effectiveness of alternative implementation strategies.

Implementation was typically considered the remit of the qualitative researchers only, taking the form of a separate chapter which was then considered in the discussion section alongside the primary study results. Hence, there was little to no consideration of how implementation would impact on the economics of the intervention. For example, Little et al. (2014) undertook an RCT to investigate streptococcal management in primary care which included a nested qualitative study

and economic evaluation (63). The qualitative study gathered GP, nurse and patient views regarding the challenges associated with the use of streptococcal test in primary care. However, these data were not then used to consider the economics of alternative implementation strategies or to test the robustness of their results to alternative assumptions regarding implementation.

Clear recommendations for implementation and future work

No studies included within the review specified implementation as a primary objective of their study. However, twenty-three of the studies referred to implementation within their specification of the study objectives as an issue for consideration. Thirty-three studies considered implementation in their discussion section only. Twenty-one of the studies included provided clear recommendations on implementation (Table 4). For example, Whitaker et al. (2016) suggested that a future economic evaluation of interventions to reduce unwanted pregnancies in teenagers adopt a "multi-agency perspective", due to the potential cost impact of interventions on, not only health, but social care providers also (59). Surr et al. (2020) evaluated the use of Dementia Care Mapping (DCM) to reduce agitation and improve outcomes in care home residents with dementia (64). This was a pragmatic RCT of a complex intervention, which included a process evaluation. The intervention was not found to be clinically- or cost-effective. However, the process evaluation identified a significant challenge in adherence to the intervention – 10% of care homes failed to participate at all in the intervention, and only 13% adhered to the intervention protocol over the required period to an acceptable level. Two homes withdrew from the study – one citing a personal belief in the ineffectiveness of the intervention. Therefore, recommendations included considering alternative modes of implementation which were not reliant on care home staff for delivery. The discussion of implementation as an issue for "further research" was reported in twenty-two of the studies included (Table 4).

Table 3: Proctor et al. (2012) checklist

		1. Care or quality gap	2. Evidence-based practice	3.a Theoretical justification	4. Stakeholder engagement	5. Setting	6. Implementation strategy	7. Team expertise	8. Study design	9. Measurement	10. Policy/funding environment
Campbell et al. (2014) **(65)**	Cardiac MRI in ischaemic cardiomyopathy	✓	✓	✓	×	×	×	×	✓	×	×
Hood et al. (2014) **(66)**	Probiotics for Antibiotic-Associated Diarrhoea	✓	✓	✓	✓	×	×	✓	✓	×	×
Livingston et al. (2014) **(67)**	Coping strategies for carers of people with dementia	✓	✓	✓	✓	×	×	✓	✓	×	✓
Bonell et al. (2015) **(58)**	Anti-bullying programme	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
Freeman et al. (2015) **(68)**	Testing kits for Crohn's disease	×	✓	✓	×	×	×	×	✓	×	×
Guthrie et al. (2015) **(69)**	Impact of NIHR HTA programme	×	✓	✓	✓	×	×	×	×	×	×
Michie et al. (2015) **(70)**	Taxonomy of behavioural change techniques	✓	✓	✓	✓	×	×	✓	✓	×	×

		1. Care or quality gap	2. Evidence-based practice	3.a Theoretical justification	4. Stakeholder engagement	5. Setting	6. Implementation strategy	7. Team expertise	8. Study design	9. Measurement	10. Policy/funding environment
Richardson et al. (2015) **(71)**	Screening for psychological and mental health issues in young people	✓	✓	✓	×	×	×	✓	✓	×	✓
Bailey et al. (2016) **(72)**	Web-based sexual health app	×	✓	✓	✓	✓	×	✓	✓	×	✓
Field et al. (2016) **(73)**	Lung cancer screening	×	✓	✓	✓	×	×	✓	✓	×	✓
Fortnum et al. (2016) **(74)**	School-entry hearing test screening	✓	✓	✓	✓	×	×	✓	✓	×	×
Freeman et al. (2016) **(68)**	My5-FU assay monitoring in chemotherapy patients	✓	✓	✓	×	×	×	×	✓	×	×
Jackson et al. (2016) **(75)**	Uptake of immunisation in Travelling and Gypsy communities	×	✓	✓	✓	✓	×	✓	✓	×	✓

		1. Care or quality gap	2. Evidence-based practice	3.a Theoretical justification	4. Stakeholder engagement	5. Setting	6. Implementation strategy	7. Team expertise	8. Study design	9. Measurement	10. Policy/funding environment
Parry et al. (2016) **(76)**	CBT therapy for fear of falling in older people	×	✓	✓	✓	×	×	✓	✓	×	×
Paton et al. (2016) **(77)**	Improving outcomes for people with mental health crises	×	✓	✓	×	×	×	✓	✓	×	✓
Tufail et al. (2016) **(78)**	Diabetic retinopathy image assessment software	✓	✓	✓	×	×	×	✓	✓	×	×
Whitaker et al. (2016) **(59)**	Programmes to reduce unintended pregnancies	✓	✓	✓	✓	×	×	✓	✓	×	✓
Birrell et al. (2017) **(79)**	Real-time influenza modelling	×	✓	✓	×	×	×	×	×	×	×
Flowers et al. (2017) **(80)**	Behavioural change programme	×	✓	✓	×	✓	×	✓	✓	×	✓

		1. Care or quality gap	2. Evidence-based practice	3.a Theoretical justification	4. Stakeholder engagement	5. Setting	6. Implementation strategy	7. Team expertise	8. Study design	9. Measurement	10. Policy/funding environment
Melendez-Torres (2017) **(81)**	Beta-interferon and glatiramer acetate for treating multiple sclerosis	✓	✓	✓	×	×	×	×	×	×	×
Snooks et al. (2017) **(82)**	Assessment of protocols for older people following a fall	×	✓	✓	✓	×	×	✓	✓	×	✓
Soomro et al. (2017) **(83)**	Surveillance for small renal tumours	✓	✓	✓	✓	✓	×	×	✓	×	×
Thomas et al. (2017) **(84)**	Breathing retraining exercises in asthma patients	✓	✓	✓	✓	×	×	✓	✓	×	×
Watson et al. (2017) **(85)**	Family and social network intervention for young people who misuse	×	✓	✓	✓	×	×	✓	✓	×	×

		1. Care or quality gap	2. Evidence-based practice	3.a Theoretical justification	4. Stakeholder engagement	5. Setting	6. Implementation strategy	7. Team expertise	8. Study design	9. Measurement	10. Policy/funding environment
	drugs and alcohol										
Waugh et al. (2017) **(86)**	Spot protein-creatinine ratio and spot albumin-creatinine ratio to assess pre-eclampsia	✓	✓	✓	×	×	×	×	✓	×	×
Welton et al. (2017) **(87)**	Screening strategies for atrial fibrillation	×	✓	✓	×	×	×	×	✓	×	×
Williams et al. (2017) **(88)**	Intervention	✓	✓	✓	✓	×	×	✓	✓	×	×
Avenell et al. (2018) **(89)**	Timing of surgical intervention for developmental dysplasia of the hip	✓	✓	✓	×	✓	×	×	✓	×	×
House et al. (2018) **(90)**	Self-management in adults with type	×	✓	✓	✓	×	×	✓	✓	×	×

		1. Care or quality gap	2. Evidence-based practice	3.a Theoretical justification	4. Stakeholder engagement	5. Setting	6. Implementation strategy	7. Team expertise	8. Study design	9. Measurement	10. Policy/funding environment
	2 diabetes and learning difficulties										
McClurg et al. (2018) **(90)**	Abdominal massage for neurogenic bowel dysfunction in multiple sclerosis	✓	✓	✓	✓	×	×	✓	✓	×	×
Paleri et al. (2018) **(91)**	Gastronomy tube feeding in chemoradiation patients	✓	✓	✓	✓	×	×	✓	✓	×	×
Peron et al. (2018) **(92)**	Colposcopy techniques for assessing cervical abnormalities	×	✓	✓	✓	✓	✓	✓	✓	✓	×
Richards et al. (2018) **(62)**	Psychological care in cardiac rehabilitation	×	✓	✓	✓	×	✓	✓	✓	✓	×

		1. Care or quality gap	2. Evidence-based practice	3.a Theoretical justification	4. Stakeholder engagement	5. Setting	6. Implementation strategy	7. Team expertise	8. Study design	9. Measurement	10. Policy/funding environment
Saramago et al. (2018) **(93)**	Pre-natal testing feteal rhesus D status	×	✓	✓	×	×	✓	✓	✓	✓	×
Seguin et al. (2018) **(60)**	Pre-natal testing feteal rhesus D status	×	✓	✓	✓	✓	×	✓	✓	×	✓
Allan et al. (2019) **(94)**	Self-sampling kits for HIV testing	✓	✓	✓	✓	×	×	✓	✓	×	×
Griffin et al. (2019) **(95)**	An intervention to improve outcomes in falls in dementia	×	✓	✓	✓	✓	×	✓	✓	×	×
James-Roberts et al. (2019) **(96)**	Support package for excessively crying infants	×	✓	✓	✓	×	×	×	✓	×	×
Madan et al. (2019) **(97)**	Behaviour change package to prevent hand dermititis	✓	✓	✓	✓	×	×	✓	✓	×	✓

		1. Care or quality gap	2. Evidence-based practice	3.a Theoretical justification	4. Stakeholder engagement	5. Setting	6. Implementation strategy	7. Team expertise	8. Study design	9. Measurement	10. Policy/funding environment
Simmonds et al. (2019) **(98)**	Imaging or detection of osteomylelitis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Francis et al. (2020) **(61)**	Management of acute exacerbations of chronic obstructive pulmonary disease	×	✓	✓	✓	×	×	✓	✓	×	×
Surr et al. (2020) **(64)**	Demential care mapping to reduce agitation in care home residents	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 4: Checklist of additional themes relevant to implementation and economic evaluation identified in the review

	Intervention	Study type	Process evaluation	Barriers and facilitators	Quantitative evaluation of implementation	Included economic evaluation	Clear recommendations for implementation	Implementation as future work
Campbell et al. (2014)	Cardiac MRI in ischaemic cardiomyopathy	Review and model	×	✓	×	✓	×	✓
Hood et al. (2014)	Probiotics for Antibiotic-Associated Diarrhoea	Cohort	×	✓	×	×	✓	×
Livingston et al. (2014)	Coping strategies for carers of people with dementia	RCT	✓	×	×	✓	×	✓
Bonell et al. (2015)	Anti-bullying programme	RCT	×	✓	×	×	✓	✓
Freeman et al. (2015)	Testing kits for Crohn's disease	Review and model	×	✓	×	✓	✓	✓
Guthrie et al. (2015)	Impact of NIHR HTA programme	Review	×	×	×	×	×	×
Michie et al. (2015)	Taxonomy of behavioural change techniques	Methods paper	✓	✓	×	×	✓	✓
Richardson et al. (2015)	Screening for psychological and mental health issues in young people	Review and model	×	✓	×	×	×	✓
Bailey et al. (2016)	Web-based sexual health app	RCT	✓	✓	×	×	×	✓
Field et al. (2016)	Lung cancer screening	RCT	×	✓	×	✓	✓	✓
Fortnum et al. (2016)	School-entry hearing test screening	Model	×	✓	×	✓	✓	×

	Intervention	Study type	Process evaluation	Barriers and facilitators	Quantitative evaluation of implementation	Included economic evaluation	Clear recommendations for implementation	Implementation as future work
Freeman et al. (2016)	My5-FU assay monitoring in chemotherapy patients	RCT	×	✓	×	✓	×	×
Jackson et al. (2016)	Uptake of immunisation in Travelling and Gypsy communities	Qualitative interview	×	✓	×	×	✓	✓
Parry et al. (2016)	CBT therapy for fear of falling in older people	RCT	×	✓	×	×	✓	✓
Paton et al. (2016)	Improving outcomes for people with mental health crises	Review	✓	✓	×	×	×	×
Tufail et al. (2016)	Diabetic retinopathy image assessment software	Cohort study	×	×	×	✓	✓	×
Whitaker et al. (2016)	Programmes to reduce unintended pregnancies	Review and model	×	✓	×	✓	✓	✓
Birrell et al. (2017)	Real-time influenza modelling	Model	×	×	×	×	×	×
Flowers et al. (2017)	Behavioural change programme	Review	×	✓	×	×	✓	×
Melendez-Torres et al. (2017)	Beta-interferon and glatiramer acetate for treating multiple sclerosis	Review and model	×	×	×	×	×	×
Snooks et al. (2017)	Assessment of protocols for older people following a fall	RCT	×	✓	×	✓	×	×

	Intervention	Study type	Process evaluation	Barriers and facilitators	Quantitative evaluation of implementation	Included economic evaluation	Clear recommendations for implementation	Implementation as future work
Soomro et al. (2017)	Surveillance for small renal tumours	RCT	✓	✓	×	×	×	×
Thomas et al. (2017)	Breathing retraining exercises in asthma patients	RCT	✓	✓	×	×	×	✓
Watson et al. (2017)	Family and social network intervention for young people who misuse drugs and alcohol	RCT	×	✓	×	×	✓	✓
Waugh et al. (2017)	Spot protein-creatinine ratio and spot albumin-creatinine ratio to assess pre-eclampsia	Model	×	×	×	✓	×	✓
Welton et al. (2017)	Screening strategies for atrial fibrillation	Review and model	×	✓	×	✓	✓	✓
Williams et al. (2017)	Timing of surgical intervention for developmental dysplasia of the hip	RCT	×	✓	×	×	×	×
Avenell et al. (2018)	Bariatric surgery	Review and model	×	✓	×	✓	×	×
House et al. (2018)	Self-management in adults with type 2 diabetes and learning difficulties	RCT	×	✓	×	✓	✓	×

	Intervention	Study type	Process evaluation	Barriers and facilitators	Quantitative evaluation of implementation	Included economic evaluation	Clear recommendations for implementation	Implementation as future work
McClurg et al. (2018)	Abdominal massage for neurogenic bowel dysfunction in multiple sclerosis	RCT	✓	✓	×	×	✓	✓
Paleri et al. (2018)	Gastronomy tube feeding in chemoradiation patients	RCT	✓	✓	×	×	✓	✓
Peron et al. (2018)	Colposcopy techniques for assessing cervical abnormalities	Review and model	×	×	×	✓	×	×
Richards et al. (2018)	Psychological care in cardiac rehabilitation	RCT	✓	✓	✓	✓	✓	✓
Saramago et al. (2018)	Pre-natal testing feteal rhesus D status	Review and model	✓	✓	×	✓	✓	×
Seguin et al. (2018)	Self-sampling kits for HIV testing	Review, cohort study, and model	✓	✓	✓	✓	✓	×
Allan et al.. (2019)	An intervention to improve outcomes in falls in dementia	RCT	✓	✓	×	✓	×	✓
Griffin et al.. (2019)	Management of fracture of the distal femur	RCT	✓	✓	×	✓	×	×
James-Roberts et al.. (2019)	Support package for excessively crying infants	RCT	×	✓	×	✓	×	✓
Madan et al. (2019)	Behaviour change package to prevent hand dermititis	RCT	✓	✓	×	✓	×	×

	Intervention	Study type	Process evaluation	Barriers and facilitators	Quantitative evaluation of implementation	Included economic evaluation	Clear recommendations for implementation	Implementation as future work
Simmonds et al. (2019)	Imaging or detection of osteomylelitis	Review	×	×	×	×	×	×
Francis et al.. (2020)	Management of acute exacerbations of chronic obstructive pulmonary disease	RCT	✓	✓	✓	✓	✓	✓
Surr et al.. (2020)	Demential care mapping to reduce agitation in care home residents	RCT	✓	✓	×	✓	✓	✓

2.7 Discussion

The extent to which implementation was formally considered varied among studies. Methods for examining implementation ranged from single stakeholder engagement events to the more comprehensive process evaluation. There was no obvious pattern as to whether approaches to implementation had evolved over recent years. Approximately half of the studies included an economic evaluation. However, it was uncommon for the economic analyses to incorporate issues relating to implementation. Where issues relating to implementation *were* included in the economic evaluation, this was limited to additional costs only. Where implementation of an intervention was considered more generally, such as in the process evaluation utilised in the Surr et al. (2020) study, they found that it was difficult to determine if the lack of effectiveness of the intervention was a result of an inherent lack of efficacy in the intervention itself or due to implementation challenges. This highlights the need to consider implementation alongside the evaluation of a health technology throughout the design and evaluation lifecycle.

Current MRC guidance on developing and evaluating complex interventions stresses the importance of considering development, feasibility/piloting, evaluation and implementation in a cyclical sequence. Specifically, they suggest involving stakeholders in the choice of question and design of the research to ensure relevance. They also suggest taking into account context, such that benefits and costs which are not captured in study can be incorporated into the analysis. Our review would suggest that this guidance is not consistently adhered to in HTA studies over the last six years (see *Stakeholders and Setting* within the Table 3). There is no obvious trend in terms of how studies have incorporated implementation issues over time. A potential reason for this lack of consistency is perhaps that, although guidance is provided by the MRC on *what* to include within an evaluation of a complex intervention, there is little guidance on *how* this should be included.

The Proctor et al. (2012) checklist provides a set of key issues which need to be considered when undertaking an implementation study. This review has assessed NIHR HTA studies over the last six years which have included implementation. Although the purpose of these studies was not explicitly to undertake an implementation study, it is worth considering to what extent issues relating to the implementation of a health technology had been included within the study, based on the checklist suggested by Proctor et al. (2012). Our findings suggest that the studies identified in our review haven't fully addressed implementation and that they need to go further. The necessary elements, such as team expertise, are often already available within the project team. What is required is guidance as to how quantitative and qualitative methods can be integrated, alongside early stakeholder engagement, so as to allow for implementation to be woven into every stage in the evaluation.

Methods for economic evaluation are well established for assessing the value for money of competing interventions, given a fixed budget constraint for the healthcare system. However, an intervention which appears highly cost-effective based on these cost-effectiveness methods as they are applied to simple interventions, may no longer be cost-effective once the process of implementation is considered. This is partly due to the impact complex interventions can have on both other services within the same disease area (e.g., acute treatment versus rehabilitation, patient pathway and organisational challenges, etc.), and also on non-health sectors (e.g., education, justice, defence, etc.). The need to consider how the costs and benefits of health technologies fall on difference sectors, and budgets, reinforces the need for economic evaluation which considers these trade-offs simultaneously. The question of whether costs "unrelated" to an intervention ought to be included within an economic evaluation remains a contentious issue (99). For example, mechanical thrombectomy is a costly, but cost-effective, treatment available for patients with acute ischaemic stroke (100). Should the initial fixed capital costs of the comprehensive stroke unit and staff training which is required to undertake this procedure be included within an

economic evaluation, or just the per procedure variable costs? Drummond argues that if health benefits arising from an intervention are projected over an individual's lifetime, then all health care costs should similarly be projected (99). The recommended approach here would be to annuitize the initial capital cost over the useful life of the asset to produce an equivalent annual cost. However, we still have the challenge of how to capture healthcare costs attributable to different budget holders within a single economic evaluation. Indeed, Wildman et al (2019) suggest that new funding models may be required to address the challenge of matching benefits and opportunities costs which fall on different sectors when implementing complex interventions (101).

The preferred measure for estimating clinical benefits from a health economic evaluation perspective is the Quality-adjusted Life-year (QALY). However, the costs and benefits of competing healthcare interventions are not always sufficiently captured within a QALY outcome. This is particularly an issue when considering the implementation of a complex intervention, where multiple outcomes may be relevant to multiple stakeholders. Methods for economic evaluation which do not reply upon the QALY are available, including cost-effectiveness, cost-consequence, multicriteria decision analysis (MCDA) and discrete choice experiments (DCEs). However, these methods are not without their limitations and have been discussed extensively elsewhere (102, 103).

In addition to the barriers imposed by implementation costs, and the problem of determining which outcomes ought to be considered, further barriers to implementation remain. These include issues relating to the design of the healthcare system and the political environment in which these decisions take place. Smith et al (2017) suggest a range of solutions for addressing barriers to implementation which go beyond cost-effectiveness analysis (104). Among these are the need to model and disaggregate a range of potential outcomes, depending on alternative

implementation scenarios and system configurations, the use of qualitative and quantitative evaluation techniques, and the involvement of the public in the decision-making process.

While not utilised in any of the studies included in this review, existing methods are available for estimating the Value of Implementation within an economic evaluation (4, 5, 45). These typically focus on either estimating the potential cost-effectiveness of alternative implementation strategies, the trade-off between directing resources towards further research or towards further implementation, or establishing a "break-even" level of implementation at which an intervention may be cost-effective. However, these methods do not consider the initial challenge of deciding what outcomes ought to be included when attempting to incorporate implementation issues into the economic evaluation of a complex intervention, nor how these outcomes should be evaluated. While useful, these methods tackle only a subset of the issues relating to implementation, and are designed to be utilised *following* a cost-effectiveness analysis. We argue that we need to understand the potential challenges of implementation before we begin an economic evaluation so that these issues can be incorporated into the analysis.

More descriptive methods are also being developed to aid the economic evaluation of implementation. Anderson et al. (2016) advocate for a more "realist" approach to economic evaluation where, rather than a focus on "measurement", the focus is on understanding what works, for whom, and in what circumstances(105, 106). More recently, McMeekin et al. (2017) demonstrated the use of conceptual modelling alongside economic evaluation to explore the relationship between the disease, treatment, and other potential mediators which impact on the "success" of an intervention (107). Both of these methodologies are contrasted with a more "black-box" approach to economic evaluation. Dopp et al. (2019) developed a framework for "mixed-method economic evaluation" in implementation science, highlighting the

benefits to implementation science researchers from undertaking economic evaluations with context-specific information capable of informing the implementation process (46). Each of these tools constitute another piece in the puzzle of integrating implementation within economic evaluation.

The implementation of health technologies in a complex problem. As such, it is unlikely that a single new methodology or perspective will address all the potential challenges associated with implementation. However, the incorporation of implementation issues into economic evaluation provides one route by which we can begin to address this problem and produce research which is more useful to decision-makers in a "real world" setting.

Economic evaluations are increasingly incorporated within clinical trials with the aim of supporting the reimbursement decision making process (108). Analogous to the introduction of economic evaluation into clinical trials, we believe that economic evaluation should play a key role in guiding the process of implementing new interventions into routine practice.

THE NIHR HTA programme is only one funder of clinical research within the UK. An extensive search of other databases may have identified methods not included within our review. However, for pragmatic purposes, and due to the prominent role played by the NIHR HTA programme in setting the research agenda in the UK, we chose to limited our search to this database only. We limited our search to studies which included the word "implementation" within the title or abstract. There are a range of terms which may relate to implementation – e.g., capacity, acceptability, stakeholder, etc. However, as our aim was to capture how any of these issues relate specifically to the challenge of implementation, we think the choice to focus on this term is reasonable. It is a limitation of this study, but also a key point, that no guidance is available for evaluating how implementation was been incorporated within an HTA.

To facilitate better implementation of research findings, further guidance will be required to help researchers decide how implementation ought to be considered within an economic evaluation from the outset and how these data should be analysed.

2.8 Conclusion

There are currently a variety of approaches available to incorporate implementation within a health technology assessment. While they all provide some insight into the issues surrounding implementation, they do not go far enough in terms of evaluation and giving recommendations on specific implementation strategies. Furthermore, the issues of economic evaluation and implementation are typically considered in isolation – with implementation factors only considered after the economic evaluation has taken place. Given the MRC's warning that an evaluation which does not include a "proper consideration of the practical issues of implementation will result in weaker interventions", this is a surprising finding (49).

Our review has demonstrated a lack of consistency in how implementation has been incorporated within NIHR HTA-funded research and, hence, a need for further guidance in this area. We argue that implementation ought to be considered early in the evaluation of a complex intervention. Furthermore, that implementation and economic evaluation ought to be integrated, such that an appreciation of the economic implications of implementation issues are considered iteratively throughout the evaluation process. We recommend a more strategic approach to considering implementation – plan ahead, collect data which will allow for a quantitative analysis, which can be supplemented by qualitative work to inform implementation. This can conveniently be done within the economic evaluation framework.

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests: The authors declare that they have no competing interests.

Funding:

This work was not funded.

Authors' contributions:

RH: design, data extraction and analysis, manuscript preparation.

KB: design, independent validation of review (10% sample), comments on final manuscript.

OW: design, independent validation of review (10% sample), comments on final manuscript.

All authors read and approved the final manuscript

Acknowledgements

Not applicable

Authors' information (optional)

The main author is a research associate in Health Economics and Health Technology Assessment within the Institute of Health and Wellbeing at the University of Glasgow. He is undertaking a PhD on methods for incorporating implementation within the economic evaluation of health technology assessments.

Chapter 3: What methods are currently available for incorporating implementation considerations within the economic evaluation of health technologies? A systematic review

3.1 Foreword

Our initial literature review (Chapter 2) was designed to summarise which methods were currently being used to incorporate implementation alongside the economic evaluation of health technologies. I found that methods were available, but that they were infrequently and inconsistently applied in practice. This was surprising, not only because of MRC and NICE guidance suggesting the consideration of implementation, but also because of my, and my supervisors', own knowledge of the literature. For this reason, I sought to review any and all methods available for considering implementation alongside economic evaluation. This allowed me to map out the methods available in this area, describe what problem these methods were designed to address, and identify what is still missing from the available literature.

3.2 Title, authorship, and publication details

Heggie, R., Boyd, K., Kamaruzaman, H., Wu, O. (2021) What methods are currently available for incorporating implementation considerations within the economic evaluation of health technologies? A systematic review.

This article has been prepared for submission to the journal Implementation Science. The overall work has been led by me and I take full responsibility for it. In this chapter, I use the terms 'we' and 'our' to recognise the contribution of all authors.

What methods are currently available for incorporating implementation considerations within the economic evaluation of health technologies? A systematic review

Mr. Robert Heggie[1], Dr. Kathleen Boyd [1], Miss Hanin Farhana Binti Kamaruzaman [1], Professor Olivia Wu[1]

[1] Health Economics and Health Technology Assessment (HEHTA), Institute of Health and Wellbeing, University of Glasgow, UK.

Corresponding author: Robert Heggie, Health Economics and Health Technology Assessment (HEHTA), Institute of Health & Wellbeing, University of Glasgow, 1 Lilybank Gardens, Glasgow G12 8RZ. Telephone: 0141 330 3047. Robert.Heggie@glasgow.ac.uk.

3.3 Abstract

Background

When clinically effective, cost-effective health interventions are not fully implemented into clinical practice, population health suffers. Economic factors are one of most commonly cited reasons for sub-optimal implementation. Despite this, implementation and economic evaluation are not routinely evaluated in conjunction with one another. This review sought to identify and describe what methods are available for researchers to incorporate implementation within economic evaluation, how these methods differ, when they should be used, and where there are gaps remaining.

Methods

We conducted a systematic literature review, using a pearl-growing approach to identify studies. References and citations were identified using Web of Science and SCOPUS. We included for review any study which contained terms relating to economic evaluation and a series of implementation-related terms in the title or abstract. The search was conducted and validated using two independent researchers.

Results

Our review identified 33 unique studies which included a methodology for combining implementation and economic evaluation. The methods identified could be categorised into four broad themes – i) policy cost-effectiveness approach (11 studies), ii) Value of Information and Value of Implementation approach (11 studies), iii) study design approach (7 studies), and iv) costing of systems change approach (4 studies). We identified a trend over time from methods which adopted the policy cost-effectiveness approach towards methods which considered the trade-off between the Value of Information and Value of Implementation. More recently, methods have been developed to inform study design and to define, measure and

cost individual components of the implementation process for use in economic evaluation.

Conclusion

Our review identified a range of methods currently available for researchers considering implementation alongside economic evaluation. There is no single method or tool which can incorporate all the relevant issues to fully incorporate implementation within an economic evaluation. Instead, there are a suite of tools available, each of which can be used to answer a specific question relating to implementation. Researchers, reimbursement agencies, national and local decision-makers need to consider how best to utilise these tools to improve implementation.

3.4 Background

Any health intervention is only as good as its implementation. Delayed or insufficient implementation of clinical- and cost-effective health technologies leads to poorer health outcomes for patients and the sub-optimal use of scarce resources for national health services. It is well documented that potentially valuable health interventions often fail to achieve widespread implementation (13). There are many reasons why implementation may be sub-optimal. However, one of the most commonly cited reasons is cost (17).

The value of a health technology is typically assessed in the UK using a cost-utility framework. Using this approach, the additional cost of a technology is compared with the additional utility obtained, where utility is most commonly measured as the quality-adjusted life-years (QALYs) gained. If the cost-per-QALY gained if below an acceptable threshold, typically between £20,000-30,000 in the UK, the technology is considered cost-effective. However, the cost-utility framework was developed during a time when reimbursement agencies, such as the National Institute for Health and Care Excellence (NICE), typically assessed pharmaceutical interventions. However, with the growing use of companion diagnostics, medical devices and AI-assisted decision making, health interventions in a clinical setting are becoming increasingly "complex". As such, it is necessary to consider how these technologies will be implemented in clinical practice.

The Medical Research Council (MRC) recently issued guidance which recommends that implementation should be considered alongside economic evaluation in the assessment of health technologies (30). However, a recent review found that research which incorporates implementation within economic evaluation is not typically included within studies funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme (100). An update to the NICE guidance for technology appraisal in 2022 placed increased emphasis on additional

costs associated with implementation, stating that an evaluation should include the full additional costs associated with introducing a technology (33).

Tools have been developed over the past two decades to help researchers build implementation into the economic evaluation of health technologies. However, a recent review found that there was little consistency in how implementation has been incorporated into health technology assessments funded by the NIHR between 2013 to 2019 (100). Despite a lack of formal guidance from reimbursement agencies and funders, methodological work in this area continues. In this review, we aim to map out the methods currently available for incorporating implementation within the economic evaluation of health technologies.

3.5 Methods

We undertook a systematic literature review, using a "pearl-growing" (also known as 'Citation mining' or 'Snowballing') methodology to identify relevant studies (109, 110). Compared with a traditional "database searching" approach, the pearl-growing approach has been shown to be more reliable for identifying studies from obscure or disparate sources (111, 112).

The pearl growing approach to systematic review involved the following 6 steps (113). In step 1, we identified a specific study or article (the "pearl"). The choice of initial pearl was based upon consultation with researchers experienced in economic evaluation alongside implementation and on the prominence of this study within this field of research. Our choice of initial pearl was *"The Value of Implementation and the Value of Information: Combined and Uneven Development.* Medical Decision Making. 2008, Fenwick E, Claxton K, Sculpher M (5)*".* This study played a seminal role in the development of this area of research and is typically cited in any methodological study on the topic of implementation within economic evaluation. In step 2, we used Web of Science to identify and extract the citations and references of the initial pearl into a

reference manager. In step 3, we then applied pre-defined inclusion and exclusion criteria for studies to produce a set of studies suitable for inclusion in the review. Duplicate results were removed. In step 4, the citations and references of these studies were then extracted to identify further pearls and the inclusion/exclusion criteria were applied again. This process was repeated until the pearls retrieved provided diminishing relevance to our research question. In step 5, a retrospective manual search of all of the pearls included for review was conducted to mitigate against user or software error. Finally, in step 6, we repeated steps 1-5 using our initial pearl on the SCOPUS database to ensure all studies cited or referenced by our initial pearl were obtained. The process is illustrated in the supplementary material (Figure 3 and 4).

Criteria for inclusion of studies

We conducted a scoping review of Google Scholar to identify the key terms most commonly used within the literature on implementation within economic evaluation. Based on the results of this review, we chose to include in our systematic review any studies which included within the title the following terms:

"*implement**" OR "*reconfiguration*" OR "*chang**" OR "*set-up*" OR "*uptake*" OR "*utilisation*" OR "*capacity*".

Any study which included these terms within the title were included for abstract review. Any study which included the following terms in the abstract were included for full manuscript review:

"*economic**" AND "*implement**" OR "*reconfiguration*" OR "*chang**" OR "*set-up*" OR "*uptake*" OR "*utilisation*" OR "*capacity*".

Following full manuscript review, a study was included within our systematic review if it described a methodology for incorporating implementation issues within the economic evaluation of a health technology. We included studies published over any time period.

Criteria for exclusion of studies

No exclusions were made based on participants, interventions, comparisons, outcomes or study design. As the purpose of this review was to identify currently available methodologies, no quality assessment of the identified studies was undertaken. Reviews and editorials were excluded. For practical reasons, non-English studies were excluded from the review. For the purpose of validation, one additional independent researcher applied the inclusion/exclusion criteria used in the pearl-growing process to the full set of studies identified in the search.

Database searched

We identified references and citations using Web of Science and SCOPUS (114).

Data extraction

All studies identified were exported to Endnote X9.3.3. Full manuscripts were reviewed to assess the content of the methodology utilised in the study. Content was assessed in terms of the approach used to consider implementation alongside economic evaluation. For the purpose of validation, one additional independent researcher assessed the content of each study to identify the approach to implementation utilised.

Data synthesis and presentation

A content analysis was employed to identify and organise common themes (or approaches) in how implementation was incorporated alongside economic evaluation in the methodologies identified in our review. We described what methods were

available, how these methods differed from one another, when they should be used, and where there are gaps remaining. Data were extracted and presented in tabular form (Table 5).

3.6 Results

Our search identified 33 unique studies for inclusion in our systematic review. Based on the studies identified in our review, four distinct approaches to considering implementation were identified: policy cost-effectiveness approach (11 studies), Value of Information (VoI) and Value of Implementation approach (13 studies), study design approach (5 studies), and costing of systems change approach (4 studies). Each of the 33 studies identified fell into at least one of these categories, however, studies often overlapped a single category.

What methods are available?

Policy cost-effectiveness

One third of the studies identified adopted the policy cost-effectiveness methodology (n=11). Three of these studies used the simplest approach, developed by Sculpher et al (2000) (115). This approach involves treating the evaluation of an implementation strategy like any other new health intervention – that is, the costs and effects of the implementation strategy are compared incrementally with an alternative strategy, or with no active implementation strategy. This is typically operationalised in a simple decision tree model.

The other eight studies utilising the policy cost-effectiveness approach adopted the framework of Mason et al. (2002) (2). In contrast to the approach of Sculpher et al. (2000), this approach combines both the costs and effects associated with a health intervention, in addition to the additional costs of implementation, to estimate an overall "policy cost-effectiveness". It does this by, for example, including the

additional costs of changing clinician behaviour and scaling this up to the total eligible patient population.

Value of Information and Value of Implementation

One third of the studies identified involved utilised a method developed by Fenwick et al. (2008) (n=11). This approach built on the previous policy cost-effectiveness work of Sculpher (2000) and Mason (2002), and also the work of Hoomans et al. (2006) (116) which focused on the decision of which evidence-based guidelines to adopt, and how best to implement them. The methods available until this point typically focused on the cost-effectiveness of specific implementation policies. Fenwick et al. (2008) was the first to consider the trade-off between the value of increasing implementation (i.e., policies to improve uptake) compared with the value of increasing information (i.e., further research to reduce decision uncertainty). They did this by considering four possible "states of the world", where both information and implementation could either be perfect or at current levels, and the expected benefit of moving between states could be explicitly trade-off for decision-makers.

Based on the work of Hoomans et al. (2006) and Fenwick et al. (2008), a single Value of Implementation framework was developed by Walker et al. (2014) (4). This was distinct from the combined Value of Information and Value of Implementation framework, for the context where further research is not considered, and the focus is on achieving a specific level of implementation. The Value of Implementation framework, developed by Walker et al. (2014), was then extended by Johannesen et al. (2020) to subcategorise the total value of perfect implementation to estimate the relative value of eliminating different sources of sub-optimal implementation (117).

All the methods for estimating the Value of Implementation identified so far have assumed that the marginal costs and benefits associated with an intervention remains constant regardless of the level of uptake achieved. Wright et al. (2020) (118)

extended the framework developed by Walker et al. (2014) to allow for the costs and benefits of an intervention to vary depending on the level of implementation. There are many reasons why costs and benefits would be expected to vary in practice, such as the need for initial capital outlays, capacity constraints or the existence of a learning curve for the delivery of a new procedure.

Study design

When reimbursement agencies consider a potentially valuable health technology with significant decision uncertainty, they face the question of whether to approve the technology or recommend further research. Value of Information and Value of Implementation methods can be used to inform these decisions. However, traditional VoI methods assume that the benefits of further information would be realised through full and immediate implementation. This is unlikely to be the case in health care provision (119-122).

The dynamic relationship between research and implementation was first considered by Fenwick et al. (2008), in the form of the "realisable" expected value of perfect information (EVPI) – that is, the value of research which is realisable without actively undertaking strategies to increase implementation. This makes the simplifying assumption that information alone does not impact implementation. This assumption is unrealistic and is relaxed in sensitivity analysis. The "realisable" EVPI is positive if new information increases implementation, equal to EVPI if it leads to perfect implementation, and negative if it decreases implementation. Willan et al. (2010) built on this relationship between information and implementation to capture the impact this can have on the expected value of sample information (EVSI) and the cost of future trials (42). Thus, they provide a framework for informing research decisions and optimal sample size calculations, allowing for imperfect implementation. Andronis et al. (2016) developed a non-parametric approach for tackling the same problem, suggesting that the applicability of Willan's method is constrained by the fact that

their approach assumes outcomes (e.g., net monetary benefit, NMB) are normally distributed (123).

While theoretical models are available, Grimm et al. (2017) highlight that the VoI methods used in practice typically do not consider that new information is likely to impact implementation (124). They extend the previous work in this area by incorporating diffusion curves to model future implementation, and by basing these curves on expert elicitation, rather than assuming that implementation is solely a function of strength of evidence (as in previous methods).

Study design for local quality improvement programmes may require a different approach than conventional clinical trials (41). One reason for this is that large clinical trials aim to estimate effects for a broad general population, whereas implementation studies often need to be tailored more to a particular setting. Considering this, Cheung et al. (2014) proposed a method for sample size calculation which incorporates cost-effectiveness alongside prior knowledge from local experts (41). This approach typically required a smaller sample size compared with conventional clinical trial sample size calculations.

The choice of which costs to include, for whom these costs are relevant, and over which time horizon, is the focus of Gold et al. (2022) (17). They argue that, over a longer time horizon, all costs are variable. However, over a short time horizon, it becomes important to distinguish between fixed and variable costs – something which is typically not observed in economic evaluations of health technologies. This is necessary because the costs and benefits of an intervention may accrue to different stakeholders if significant upfront investment is required at an early stage of implementation.

Implementation challenges are often not captured using the sort of quantitative methods discussed so far in this review. To address what they regard as the "qualitative residual", Dopp et al. (2019) offered guidance on how to conduct a "mixed-methods" approach to economic evaluation in implementation research (46). They do this by demonstrating how each item of the CHEERS checklist can be addressed from a mixed-methods perspective – typically by complementing their quantitative findings with qualitative insights. For example, they show how qualitative interviews of participants can reinforce or contradict the cost-effectiveness results based on incremental cost-effectiveness ratios.

O'Leary et al. (2022) argue that current methods typically underestimate the resources required to implement complex interventions (125). Building further on the mixed-methods approach to economic evaluation and implementation, O'Leary et al. (2022) suggest the use of the Exploration, Preparation, Implementation, Sustainment (EPIS) framework (126) as a vehicle for bringing in a range of tools necessary to conduct a full economic evaluation of complex interventions. The EPIS framework is a conceptual model which highlights four key stages of implementation. Based on these four stages, O'Leary et al. (2022) suggest a range of existing methods for data collection and analysis which are relevant from a health economic perspective. For example, stakeholder interviews within the Exploration phase to identify their readiness to adopt a new intervention, and to identify likely barriers and facilitators. In the Implementation phase, the use of simulation methods to compare the expected outcomes in the local context with those of the overall population, with the aim of identifying potential equity issues.

Costing of systems change

Saldana et al. (2014) suggest that one reason implementation costs are not routinely considered alongside the evaluation of health interventions is that there is a lack of standardised instruments for measuring implementation costs (127). This may make it

difficult for decision-makers to compare implementation costs across mulitple potential health interventions. To this end, they developed a tool which maps costs on eight pre-specified implementation stages of a foster care programme which allows for a cost comparison of implementation strategies. While this tool was developed for use in a foster care programme, it could easily be adapted for use in the evaluation of other health interventions.

Building on the work of Saldana et al. (2014), Cidav et al. (2020) (128) developed a more general framework which combined a time-driven activity-based micro-costing (TDABC) method with the Proctor et al. (52) framework for reporting standards in implementation research. The result is a framework which allows the researcher to define *"who (personnel completing the task) does what (specific activities performed), when (timing), and how often (the frequency, intensity and/or duration of the activity)"* alongside Proctor's guidance for the naming, defining and conduction of implementation strategies (129). Together, this provides a tool for researchers to estimate resource use and cost for both a complete implementation strategy and for the distinct stages involved. These data can then be used to inform the economic evaluation of implementation strategies.

Major systems change (MSC) involves the reorganisation or reconfiguring of healthcare services, typically in the form of a centralisation of services, with a view to improving outcomes through greater specialisation. Economies of scale may mean that this can be achieved at a comparable or reduced cost. However, quality economic evaluations which incorporate the implementation cost associated with MSC are lacking (38, 130). Clarke et al. (2021) used the reorganisation of cancer services in London as a case study to develop a framework for costing the process of MSC (131). Similar to Cidav et al. (2020), this approach involves the specification of key stages in the implementation process. However, evaluation perspective is also important when considering implementation cost. To this end, Clarke et al. (2021) goes one step

further and provides guidance on which implementation costs will be relevant for which perspective – provider, payer or national. These data can then be used to inform the economic evaluation of major systems change, from the perspective of the relevant decision-maker.

While Clarke et al. (2021) focused on the costing of MSC, Hunter et al. (2018) undertook a full economic evaluation of the impact of reconfiguration of stroke services in London and Manchester (132). They used a difference-in-differences approach to estimate the change in cost and QALYs pre-and post-reconfiguration. However, in addition to presenting the results using the traditional metric of incremental cost per incremental QALY gained, they also used a Programme Budgeting and Marginal Analysis (PBMA) approach to report the results in terms of the number of QALYs gained, given a fixed budget and expected number of strokes per year for a hypothetical setting. The authors note that while a cost-per-QALY approach is more commonly utilised for economic evaluation, due to the influence of the National Institute for Health and Care Excellence (NICE), the incremental cost-per-QALY approach may not always be the most relevant to local decision-makers with a fixed budget who need to consider what return they can achieve for a given investment.

How do the methods differ from one another?

The main difference in the range of methods identified in this review is the purpose for which they were developed. While they all focus on the issue of implementation, four main approaches were identified – i) policy cost-effectiveness approach, ii) Value Information and Value of Implementation approach, iii) study design approach, and iv) costing of implementation approach. There are two distinct approaches to considering policy cost-effectiveness. The simplist approach, based on the work of Sculpher et al. (2000), involves a comparative economic evaluation of the costs and effects (e.g., QALYs, quality improvement, etc.) associated with implementing, or

increasing uptake of, a health technology. This can take the form of a simple decision tree with the costs and effects of an implementation strategy compared with an alternative implementation strategy or no further implementation. This approach is methodologically straightforward. The challenge here is quantifying the cost and effect associated with each strategy. Tools for calculated the costs associated with implementation are available and have been highlighted in this review. Similarly, tools are available for estimating the health benefit of increased implementation. However, generating these data would represent an additional task on top of the comparative evaluation of the overall impact of the implementation strategies. Therefore, while methodologically simple to employ, the data required to undertake such an analysis may be difficult and time-consuming to obtain. However, such analyses could be undertaken based on assumption and expert opinion – particularly for the purpose of determining thresholds where further implementation would (or would not) be likely to be considered worthwhile.

The second approach to considering policy cost-effectiveness, based on the work of Mason et al. (2001), involves incorporating the cost of changing a physicians behavour (e.g., the cost of implementing change per practice) in addition to the "treatment cost-effectiveness" (costs and effects per patient) of a health technology. This approach can be considered an extension of the Sculpher et al. (2000) approach, which, rather than considering the process of heath technology evaluation and implementation strategy evaluation separately, combines the two concepts to derive an overall "policy cost-effectiveness" for a health technology.

The main distinction amongst methods identified in this review is whether or not implementation is the sole purpose of the analysis, or whether this is traded-off against the value of further research. Where implementation is the focus, the Walker et al. (2014) approach is the most commonly used. Where the trade-off between information and implementation is the focus, the Fenwick et al. (2008) approach is

most commonly used. However, both methodologies have subsequently been developed further.

Some methods to consider implementation in study design, which continue in the tradition of Fenwick et al. (2008), focus on the interaction between information and implementation, and the implication this can have for realisable EVPI (e.g., the actual EVPI, given imperfect implementation), the cost of further research and optimal sample size. More recently, attention has been given to the value of incorporating qualitative methods into the study of economic evaluation and implementation (46, 125).

From a methodological perspective, Cidav et al. (2020) and Clarke et al. (2021) are similar in approach – they both seek to break down the implementation process into identifiable components, each of which can then be measured and valued for the purpose of inclusion in a full economic evaluation. The main difference between these tools is the purpose for which they would be used – the former for the evaluation of the implementation of a health intervention, the latter for the evaluation of a major systems change.

What gaps are there in the methods currently available?

There is no single method or tool which can incorporate all the relevant issues to fully incorporate implementation within an economic evaluation. Instead, there are a suite of tools available, each of which can be used to answer a specific question relating to implementation.

Current methods for considering implementation alongside economic evaluation typically focus on the value of increasing uptake of a health technology and how this compared with other objectives – such as further research. This assumes we have a well-defined health technology, ready to be scaled as required. However, prior to this

step, it is first necessary to define *how* a health technology will be implemented. Many issues which were not identified or tested in the clinical trial of a health technology may pose challenges to implementation in routine practice. For example, there may be differences relating to the clinical pathway for patients, modes of delivery, setup and training costs, or any other aspect of how the technology is delivered in practice.

While tools are available for identifying these issues within the trial setting – for example, qualitative methods –, how these tools should be combined with the tools of economic evaluation is less clear. Dopp et al. (2019) provide a first step in tackling this challenge with their guidance for mixed methods economic evaluations. However, our review did not identify any studies which had used this guidance to date. No other methods for combining qualitative and quantitative data in the economic evaluation of implementation were identified.

Table 5: Summary of type of methodological approach used in each study identified in the review

	Methodological approach			
	Policy cost-effectiveness	Value of Information and Value of Implementation	Study design	Costing systems change
Sculpher et al. (2000) **(115)**	✓			
Mason et al. (2001) **(2)**	✓			
Severens et al. (2003) **(133)**	✓			
Gandjour et al. (2005) **(134)**	✓			
Dijkstra et al. (2006) **(135)**	✓			
Wright et al. (2007) **(136)**	✓			
Fenwick et al. (2008) **(5)**		✓		
Hoomans et al. (2008)**(137)**	✓			
Hoomans et al. (2009) **(138)**	✓			
Hoomans et al. (2009) **(139)**		✓		
Hoomans et al. (2009)**(140)**	✓			
Wilan et al. (2010) **(42)**			✓	
Soeteman et al. (2011) **(141)**		✓		
Cheung et al. (2014) **(41)**			✓	
Fortney et al. (2014) **(142)**	✓			
Saldana et al. (2014) **(127)**				✓
Walker et al. (2014) **(4)**		✓		
Andronis et al. (2016) **(123)**			✓	

Whyte et al. (2016) **(45)**		✓		
Faria et al. (2017) **(143)**		✓		
Grimm et al. (2017) **(124)**			✓	
Mewes et al. (2017) **(144)**		✓		
Hunter et al. (2018) **(132)**				✓
Dopp et al. (2019) **(46)**			✓	
Cidav et al. (2020) **(128)**				✓
Eisman et al. (2020) **(145)**	✓			
Heggie et al. (2020) **(146)**		✓		
Johannesen et al. (2020) **(117)**		✓		
Wright et al. (2020) **(118)**		✓		
Clarke et al. (2021) **(131)**				✓
Gold et al. (2022) **(17)**			✓	
O'Leary et al. (2022) **(125)**			✓	
Wright et al. (2022) **(147)**		✓		
Frequency of method	11	11	7	4

3.7 Discussion

Our review identified 33 studies which included methods for considering implementation alongside the economic evaluation of health interventions. The methods identified could be broadly categorised according to the following themes – i) policy cost-effectiveness approach (11 studies), ii) Value of Information and Value of Implementation approach (11 studies), iii) study design approach (7 studies), iv) and costing of systems change approach (4 studies).

A clear trend is evident over time. The majority of early methods in this area focused on policy cost-effectiveness – a comparative analysis of the implementation strategies. This evolved into methods designed to trade-off the value of further research against the Value of Implementation (e.g. further uptake). These ideas were then used to develop tools for incorporating implementation issues into study design. More recently, methods have been developed to aid researchers in defining, measuring and costing individual stages of implementation for use in economic evaluation.

To the best of our knowledge, there are currently no reviews of methods available for considering implementation alongside economic evaluation. Roberts et al. (2019) conducted a review of the use of economic evaluation methods in implementation studies (39). They found that economic evaluation was not commonly applied within implementation studies. Furthermore, they highlighted that economic evaluations were typically conducted post-implementation, using retrospective data. This implies that economic evaluation did not play an important role in decision making regarding implementation strategies.

Our review identified guidance for a mixed method approach to economic evaluation which incorporates implementation issues (46). However, our review did not identify any examples of this approach used in practice. This may partly be explained by the

recency of this guidance. However, it is likely that further guidance will be necessary to describe how to combine qualitative and quantitative data in the economic evaluation of implementation. For example, how should we use qualitative data to inform our sensitivity and scenarios analyses? What should we do when qualitative and quantitative findings are in conflict? How can qualitative data broaden our understanding of patient "value" in economic evaluation? And how would these results be used by decision-makers?

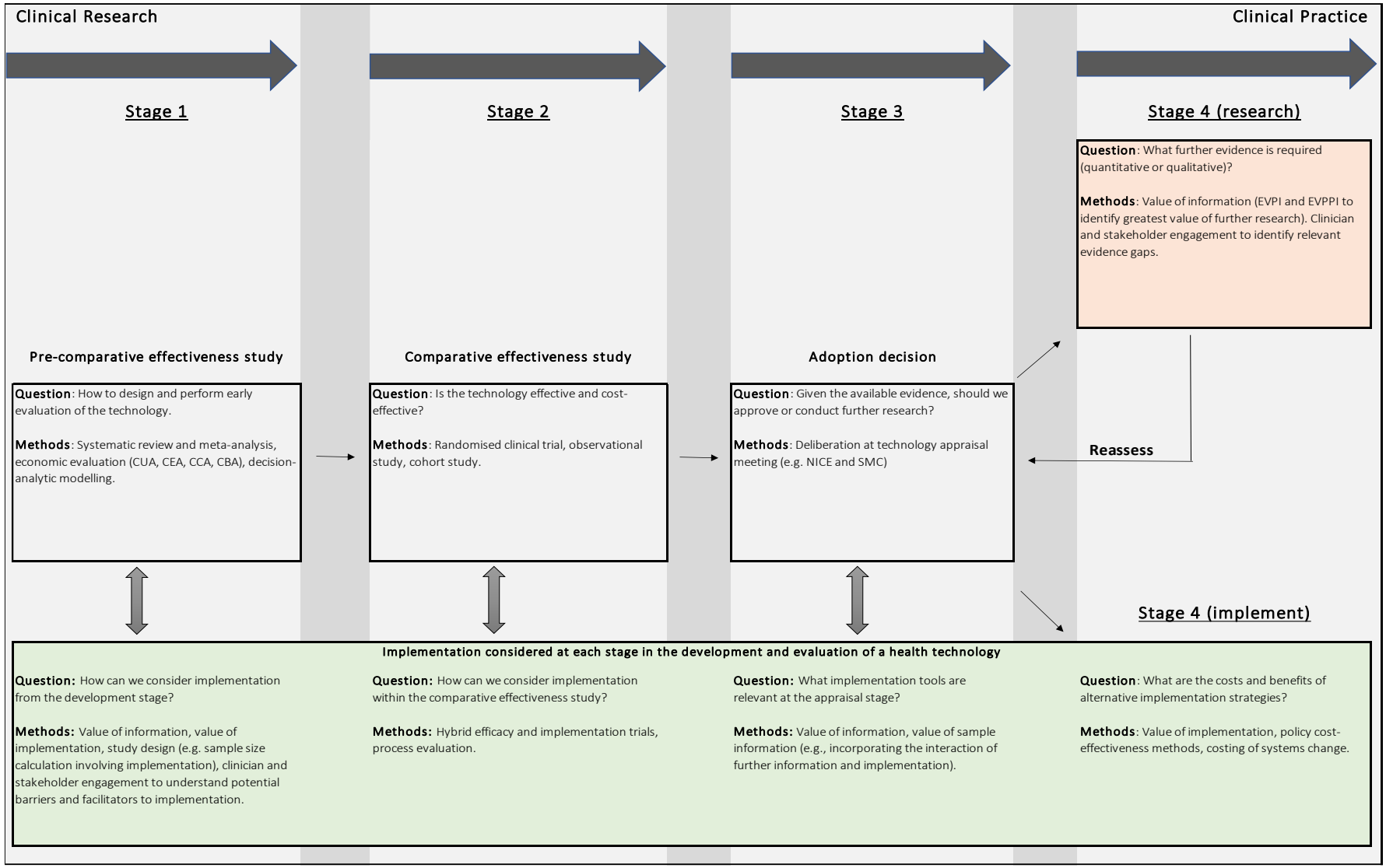
Health interventions which require a significant upfront investment can be particularly challenging to implement. One of the reasons for this is that, even when an intervention has been deemed cost-effective by a national reimbursement agency, the capital outlay required to set up the facilities necessary to deliver the intervention may come from either national or local health budget holders. These different stakeholders do not necessarily share the same priorities. They may also not have the same incentives to facilitate change. For example, a new health intervention may lead to a health improvement at the population level, but the cost may be imposed on a single local health authority. In such a scenario, the benefits are shared, but the cost is imposed on a single party. Methods to address the interest of multiple stakeholders are available (148), but further work is this area is necessary to ensure incentives are aligned among stakeholders.

Methods identified in this review typically sought to estimate the Value of Implementation using the QALY outcome as the measure of benefit. However, the benefit of competing health interventions is not always sufficiently captured within a QALY outcome – either because the QALY is not feasible to capture or not relevant in this context.

Further research is necessary to develop methods for considering the importance of implementation in the context of a complex intervention, where multiple outcomes

may be relevant to different stakeholders. Multi-criteria decision analysis (MCDA) and discrete choice experiments (DCE) provide tools whereby multiple outcomes can be traded-off and valued for the purpose of healthcare decision making. However, further guidance into how these methods should be used in economic evaluation is required (103, 149). To date, these tools have not been utilised in the economic evaluation of implementation.

Based on the findings of our review, we can summarise the methods available for incorporating implementation within economic evaluation, alongside other methods available from implementation science and economic evaluation, in a conceptual model which suggest where these methods may be most relevant for the development, evaluation and implementation of a health technology (Figure 2).



*CUA: cost utility analysis, CEA: cost-effectiveness analysis, CCA: cost-consequence analysis, CBA: cost-benefit analysis

Figure 2: Conceptual model of methods identified in our review and where they might be relevant in the development, evaluation and implementation of a health technology.

Stage 1 of the model describes the pre-comparative effectiveness study stage where the focus is on the development and early evaluation of a health technology. At this stage, where the evidence base for a health technology is still under development, Value of Information (150) and Value of Implementation methods (4) can be used to inform study design and key areas of uncertainty. Engagement with clinicians and other stakeholders at this stage can help to identify barriers and facilitators to implementation, inform and validate technology development and modelling requirements (151). Stage 2 involves the assessment of clinical- and cost-effectiveness data. In additional to the standard methods of clinical trials, observational studies and economic evaluation, methods involving hybrid effectiveness-implementation study design (152), sample size calculation methods which incorporate implementation (42), and process evaluation (20) may also be appropriate. Stage 3 represents the technology appraisal stage of the health technology assessment process. At this stage, the central question is whether to approve the technology, based on current clinical and economic evidence base, or whether to recommend further research to reduce decision uncertainty. The Fenwick et al. (2008) framework for considering the trade-off between investing in uptake or further research is particularly relevant at this stage (5).

Following this decision, the conceptual model focuses on the decision problem of implementation or further research. However, it should be noted that, as highlighted in the review, these two decision problems are not necessarily distinct and may interact with one another.

In stage 4 (implement) we can use the Value of Implementation, policy cost-effectiveness and the costing of systems change methods to estimate the costs and consequences associated with efforts to increase implementation of the technology

If the decision was taken at stage 3 to undertake further research, stage 4 (research) involves the consideration of what sort of additional evidence is required. Value of Information methods (such as the expected value of perfect and partial information) will be relevant. These analyses can be informed or supplemented with qualitative data obtained from clinician and stakeholder engagement. Once further research evidence is obtained, there is an option to return to stage 3 of the model and reassess whether to proceed with implementation or whether further research is still required to reduce decision uncertainty.

It is important that economic evaluation and implementation be considered alongside one another when evaluating a health intervention. Decision-makers need to know not only the costs and benefits associated with a health intervention, but also the challenges associated with implementation. To achieve this, health economists and implementation scientists need to work together to develop new, and implement current, methods for incorporating implementation into economic evaluation.

Our review has shown that a range of methods are currently available for researchers considering implementation alongside economic evaluation. While further research will be required to develop these methods, better coordination is also required among national reimbursement agencies and both national and local decision-makers to create an environment in which this type of research is both sought and utilised in decision making. This is necessary to ensure that the costs and benefits of a health intervention are distributed fairly and that incentives are aligned among multiple stakeholders.

3.8 Conclusion

This review has identified a range of methods available for researchers to incorporate implementation into economic evaluation. There is no single method or tool which can incorporate all the relevant issues to fully incorporate implementation within an

economic evaluation. Instead, there are a suite of tools available, each of which can be used to answer a specific question relating to implementation. Researchers, reimbursement agencies, national and local decision-makers need to consider how best to coordinate research and decision making in this area to ensure that research findings are able to incorporate and address the challenges relating to implementation.

3.9 Supplementary material

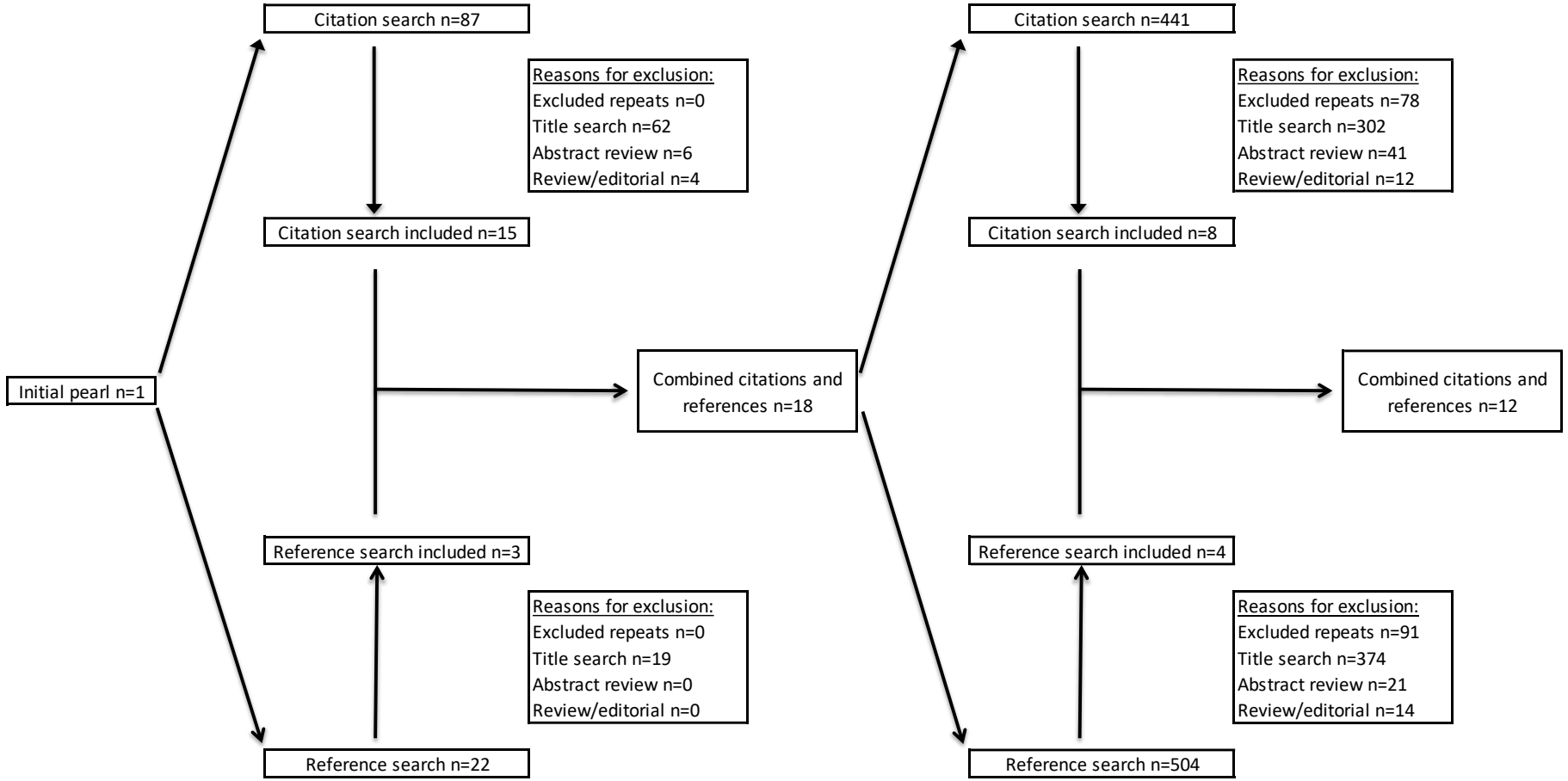


Figure 3: Flow Diagram of Pearl Growing Literature Review in Web of Science

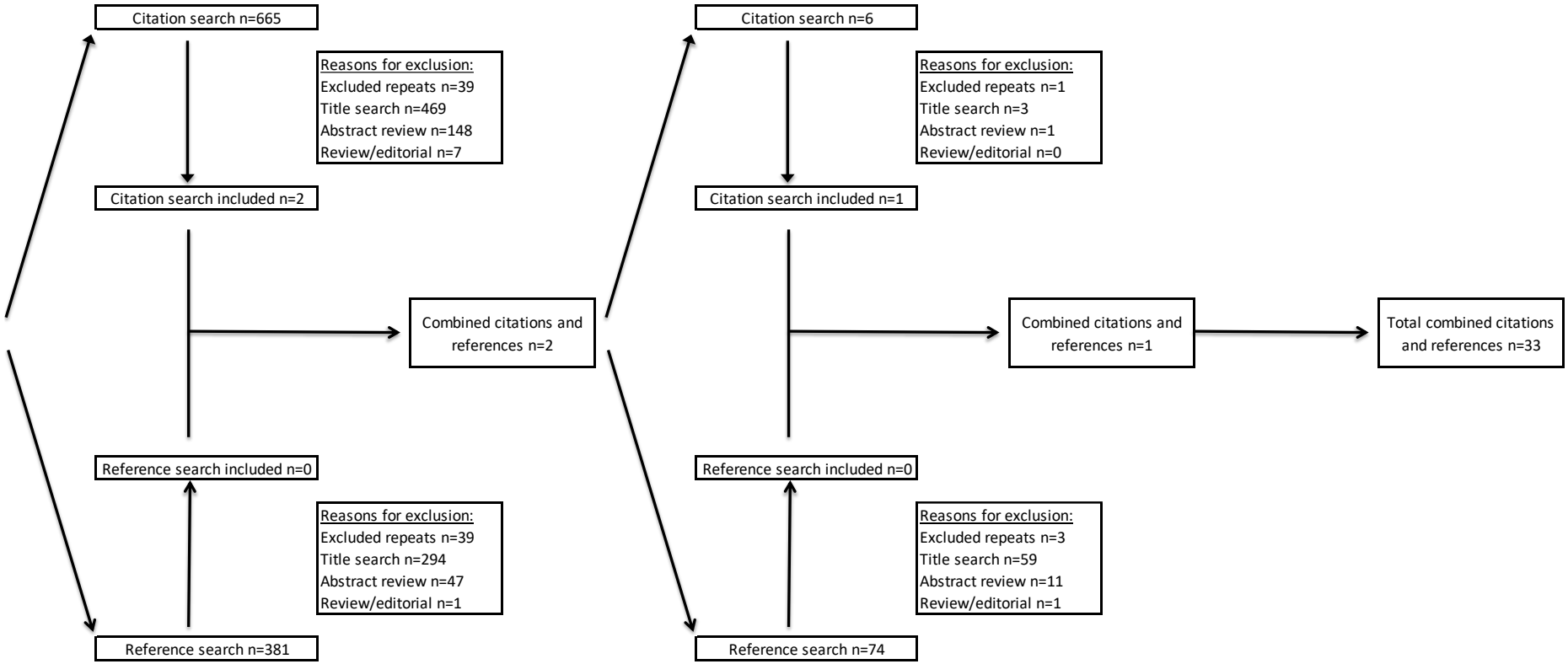


Figure 3 (continued): Flow Diagram of Pearl Growing Literature Review in Web of Science

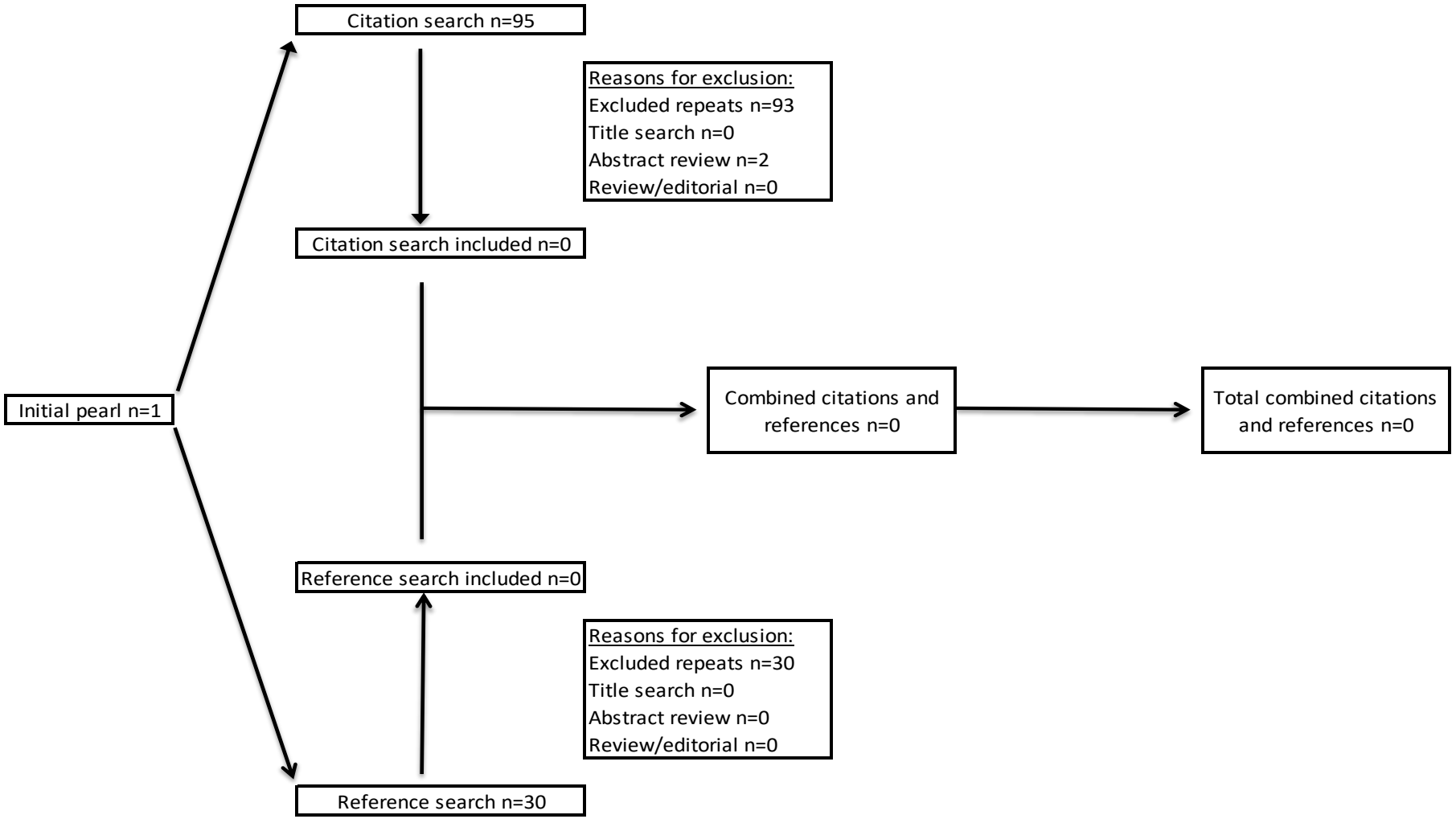


Figure 4: Flow Diagram of Pearl Growing Literature Review in SCOPUS

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests: The authors declare that they have no competing interests.

Funding:

This work was not funded.

Authors' contributions:

RH: design, search, data extraction and analysis, manuscript preparation.

HK: search, data extraction, comments on final manuscript.

KB: design, comments on final manuscript.

OW: design, comments on final manuscript.

All authors read and approved the final manuscript

Chapter 4: Mechanical Thrombectomy in Patients with Acute Ischaemic Stroke: A Cost-effectiveness and Value of Implementation Analysis

4.1 Foreword

The work in this chapter is based on a NIHR HTA funded clinical trial - the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE). I undertook a cost-effectiveness analysis of mechanical thrombectomy plus standard of care, compared with standard of care alone, in the treatment of patients with acute ischaemic stroke. I used standard recommended methods for my analysis – economic evaluation alongside a clinical trial and a lifetime extrapolation of cost-effectiveness. My analysis found that mechanical thrombectomy was likely to be cost-effective, over a lifetime horizon, based on a cost-per-QALY approach. However, following completion of this analysis, conversations with the PI on the PISTE trial made it clear to me that the implementation of mechanical thrombectomy into routine clinical practice would present a challenge. It was these conversations that sowed the seeds of my PhD.

The initial setup costs for a 24-hour access mechanical thrombectomy service was highlighted as the most saliant barrier to implementation. This included both the capital investment required to purchase the biplane angio suite necessary for mechanical thrombectomy and the configuration and cost of a dedicated workforce trained in the delivery of this procedure. I was not able to incorporate all the issues relating to the implementation of mechanical thrombectomy in my analysis. Indeed, it is unlikely that any single study could achieve this task. However, I do believe I was able to make a contribution towards addressing this challenge. More importantly, in the context of my PhD, this study provided me with the opportunity to begin to ask questions regarding how and when implementation should be considering alongside economic evaluation within the health technology assessment process.

4.2 Title, authorship, and publication details

Heggie, R., Wu, O. , White, P., Ford, G. A., Wardlaw, J., Brown, M. M., Clifton, A. and Muir, K. W. (2020) Mechanical thrombectomy in patients with acute ischemic stroke: a cost-effectiveness and value of implementation analysis. International Journal of Stroke, 15(8), pp. 881-898. (doi: 10.1177/1747493019879656) (PMID:31564243)

The overall work has been led by me and I take full responsibility for it. In this chapter, I use the terms ‘we’ and ‘our’ to recognise the contribution of all authors.

Mechanical Thrombectomy in Patients with Acute Ischaemic Stroke: A Cost-effectiveness and Value of Implementation Analysis

Robert Heggie[1], Olivia Wu[1], Phil White[2], Gary A Ford[3], Joanna Wardlaw[4], Martin M Brown[5], Andrew Clifton[6], Keith W Muir[7]

[1]Health Economics and Health Technology Assessment (HEHTA), Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
[2]Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK
[3]Division of Medical Sciences, Oxford University Hospitals NHS Trust, Oxford University, Oxford, UK
[4]Brain Research Imaging Centre, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
[6]Stroke Research Centre, UCL Institute of Neurology, University College London, London, UK
[7]St George's, University of London, London, UK
[8]Institute of Neuroscience & Psychology, University of Glasgow, Queen Elizabeth University Hospital, Glasgow, UK

Key words: Mechanical thrombectomy, cost-effectiveness, implementation, budget impact

List of figures/tables: 1. Model diagram 2. Cost-effectiveness plane 3. Cost-effectiveness acceptability curve 4. Expected value of perfect information 5. List of parameters 6. Results

Corresponding author:
Robert Heggie
Health Economics and Health Technology Assessment

Institute of Health & Wellbeing
University of Glasgow
1 Lilybank Gardens, Glasgow G12 8RZ
01413303047

Summary statement

What is already known on the topic

The clinical effectiveness of mechanical thrombectomy (MT) has been established in multiple clinical trials. Clinical trials from non-UK data have been combined with UK cost data to estimate potential cost-effectiveness of MT in a UK setting.

What this study adds

This is the first study to utilise UK clinical trial data, resource use data and cost data to estimate the potential cost-effectiveness of MT in a UK setting. Due to the significant capital costs and systems reorganisation required to deliver MT, uncertainty remains over the potential cost-effectiveness of implementation of MT into routine practice throughout the UK. This is the first study which has estimated the cost of setting-up a 24-hour MT service in the UK capable of treating the eligible population over the required 4.5 hour time from stroke onset.

4.3 Abstract

Background

Recent clinical trials have demonstrated the efficacy of mechanical thrombectomy (MT) in acute ischaemic stroke.

Aims

To determine the cost-effectiveness, value of future research and Value of Implementation of MT.

Methods

Using UK clinical and cost data from the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) trial, we estimated the cost-effectiveness of MT over time horizons of 90-days and lifetime, based on a decision-analytic model, using all existing evidence. We performed a meta-analysis of seven clinical trials to estimate treatment effects. We used sensitivity analysis to address uncertainty. Value of Implementation analysis was used to estimate the potential value of additional implementation activities to support routine delivery of MT.

Results

Over the trial period (90 days), compared with best medical care alone, MT incurred an incremental cost of £5,207 and 0.025 gain in QALY (incremental cost-effectiveness ratio (ICER) £205,279), which would not be considered cost-effective. However, MT was shown to be cost-effective over a lifetime horizon, with an ICER of £3,466 per QALY gained. The expected value of perfect information per patient eligible for MT in the UK is estimated at £3,178. The expected value of full implementation of MT is estimated at £1.3 billion over five years.

Conclusion

MT was cost-effective compared with best medical care alone over a patient's lifetime. On the assumption of 30% implementation being achieved throughout the UK healthcare system, we estimate that the population health benefits obtained from this treatment are greater than the cost of implementation.

Trial registration: NCT01745692

4.4 Background

In acute ischaemic stroke caused by large artery occlusion of the anterior circulation, mechanical thrombectomy (MT) significantly increases the proportion of patients achieving favourable outcomes at day 90 on the modified Rankin Scale (mRS) (153-160). In 2015, the European Stroke Organisation (ESO) updated guidelines for the treatment of acute ischaemic stroke to recommend the use of mechanical thrombectomy (161). In 2016, the National Institute for Health and Care Excellence (NICE) updated their guidelines to include the use of mechanical thrombectomy in the UK (154).

Mechanical thrombectomy is a highly skilled procedure undertaken predominantly in neuroscience centres. Several studies have assessed the cost-effectiveness of thrombectomy in combination with best medical care compared with best medical care alone, and concluded thrombectomy to be cost-effective (162-169) or potentially cost-saving (170-173). Best medical care includes intravenous thrombolysis with recombinant tissue plasminogen activator (IV-tPA) in the majority of cases, and in some clinical trials eligibility for IV-tPA was a mandatory inclusion criterion. Two model-based cost-utility analyses, from the perspective of the UK NHS have been carried out (165, 172). Based on meta-analysis of five RCTs, compared with best medical care alone, thrombectomy in combination with best medical care was associated with an additional £7,061 per quality adjusted life year gained (165). In the other study, based on data from an RCT conducted in the US and Europe (the SWIFT-PRIME trial), thrombectomy in combination with best medical care was reported to be associated with cost-savings of £33,190 per patient (172). However, the adoption and implementation of thrombectomy into routine practice requires additional investment in staff and capital equipment, and is also likely to require significant reorganisation of the healthcare system (174). Implementation in the UK has been limited due to combinations of staffing shortages in interventional and diagnostic neuroradiology, and the need for service reconfiguration. Most existing services

currently cover only limited working hours (175-177). It is planned that the service should expand. Currently, one study has estimated the budget impact of adopting and implementing mechanical thrombectomy in Ireland (164). Based on treatment being delivered at two centres and treating 1,340 patients over five years, the cost of implementation was estimated to be 7.2 million euros over five years.

We conducted an economic evaluation to determine the cost-effectiveness of mechanical thrombectomy in combination with best medical care compared with best medical care alone, in patients with acute ischaemic stroke. We undertook Value of Information analysis to estimate the monetary value of future research to reduce uncertainty in our estimate of cost-effectiveness. In adopting non-drug interventions into clinical practice, challenges to implementation may have an impact on cost-effectiveness. Value of Implementation analysis was used to estimate the potential value of additional implementation activities to support the delivery of mechanical thrombectomy in routine practice.

4.5 Methods

We estimated the cost-effectiveness of mechanical thrombectomy plus best medical care, compared with best medical care alone, in patients who had acute ischaemic stroke with large artery occlusive anterior circulation. Our analysis was performed over two time horizons: (i) 90-days – alongside the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) trial and (ii) lifetime – based on a decision-analytic model. The lifetime model was used to conduct one-way and probabilistic sensitivity analysis. We also estimated the potential value of future research and the Value of Implementation initiatives to support the introduction of thrombectomy in routine practice. The analysis was carried out from the perspective of the UK National Health Service (NHS) and Personal and Social Services (PSS). Costs and health benefits were discounted at 3.5% in line with national guidelines (178). Costs were expressed in UK pounds Sterling (2015/16 prices).

Within-trial analysis

The PISTE trial was a multicentre, randomised controlled clinical trial comparing mechanical thrombectomy plus best medical care including IV-tPA with best medical care including IV -tPA alone, in patients who had acute ischaemic stroke with large artery occlusive anterior circulation. Eligible patients were administered IV-tPA within 4.5 hours of stroke. Patients receiving additional mechanical thrombectomy were treated within a target time of <90 mins from IV-tPA start to arterial puncture. The primary outcome was the proportion of patients achieving functional independence mRS 0-2 at 90 days.

We conducted an economic evaluation using data from the PISTE trial. Clinical outcome at 90 days was measured by mRS score. The mRS scores were converted into health utilities using a conversion algorithm (179). Health utilities were used to calculate quality-adjusted life-years (QALYs) over 90 days. Resource use estimates collected during the trial included hospital bed days and cost of treatment with mechanical thrombectomy and best medical care. Unit costs were obtained from the literature (165, 180, 181) and applied to resource use.

Mean patient costs and QALYs were estimated by using a generalised linear model (GLM) and adjusting for potential confounding (182). We adjusted for the following covariates: age group, National Institutes of Health Stroke Scale (NIHSS) group, and baseline health utility (QALY estimates only). The appropriate family for the GLM was selected based on the results of the modified Park's test. Our final cost model was based on the log link and gamma family. Our final QALY model was based on the identity link and Gauss family. All analyses were conducted in Stata 12.1 (StataCorp). Based on the estimation of the final statistical model, the total cost and QALY difference between groups is based on the marginal prediction.

Cost-effectiveness was expressed as the incremental cost-effectiveness ratio (ICER).

We used nonparametric bootstrapping to calculate 95% confidence intervals for our estimate of the difference in mean cost and QALYs between treatment groups.

Lifetime economic model

The economic model was based on a previously published model (165) and is in line with the clinical pathway described for patients with acute ischaemic stroke who are eligible for treatment with both best medical care and mechanical thrombectomy, according to the guidance set out by NICE (National Institute for Clinical Excellence 2016) (Figure 5).

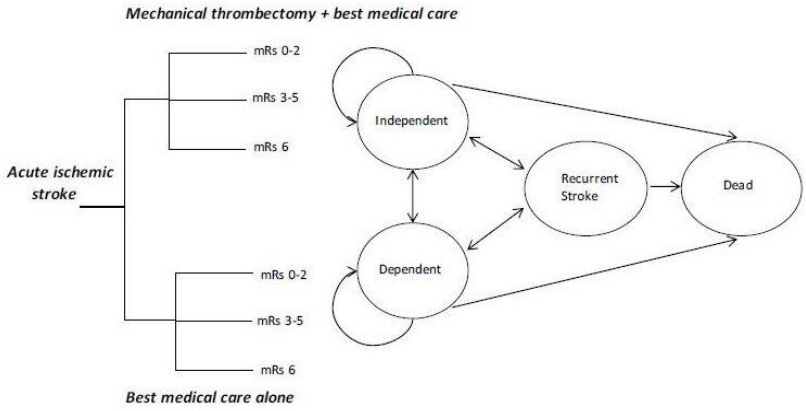


Figure 5: Schematic of decision tree and Markov model

The 90 days following stroke is represented by a decision tree. Although patients' mRS score can vary appreciably over 90 days, we assume that the mRS score recorded at 90 days represents the most appropriate measure of functional status following treatment. Hence, at 90 days, patients are assumed to enter into one of three possible mutually exclusive health states (mRS 0-2: functional independence; mRS 3-5: functional dependence; mRS 6: death). Subsequently, a four-state Markov model is used to estimate costs and outcomes beyond three months. The model runs for 80 cycles of three months (20 years).

We performed a meta-analysis to estimate the probabilities of patients resulting in the three mRS scores using data from five RCT studies published in 2015 (155-159) and two recent trials – THRACE and PISTE trials (43, 160). Transition probabilities for the Markov model were sourced from the literature (183). Table 6 presents a list of parameters used in the lifetime model. Health utility estimates were obtained from published literature (184). Unit costs were obtained from the literature and applied to the recorded resource use associated with hospitalisation (procedure and stay costs), rehabilitation and community care costs (165, 181, 185). Non-UK currencies were converted to UK currency at the cost year reported in the literature and inflated to our reference year of 2015/16 prices using the Hospital & Community health services (HCHS) index (186, 187). Further details are given in Supplementary Material.

Table 6: Point estimates, probability distributions and source of parameter estimates used in the lifetime economic model

Parameter	Point estimate	Probability distribution	Source
Decision tree*			
mRS 0-2 (Best medical care + MT)	0.57	Conditional beta distribution (α=415, β=448)	Meta-analysis
mRS 3-5 (Best medical care + MT)	0.27	Conditional beta distribution (α=322, β=541)	Meta-analysis
mRS 6 (Best medical care + MT)	0.16	Conditional beta distribution (α=126, β=737)	Meta-analysis
mRS 0-2 (Best medical care only)	0.26	Conditional beta distribution (α=264, β=611)	Meta-analysis
mRS 3-5 (Best medical care only)	0.55	Conditional beta distribution (α=456, β=419)	Meta-analysis
mRS 6 (Best medical care only)	0.19	Conditional beta distribution (α=153, β=722)	Meta-analysis
Markov model*			
Year 1			
From independent (mRS 0-2) to:			

mRS 0-2	0.955	Conditional beta distribution (α=1337, β=63)	Davis et al. (2012)
mRS 3-5	0.024	Conditional beta distribution (α=34, β=1366)	Davis et al. (2012)
Recurrent stroke	0.013	Conditional beta distribution (α=18, β=1382)	Davis et al. (2012)
Dead	0.008	Conditional beta distribution (α=11, β=1389)	Davis et al. (2012)
From dependent (mRS 3-5) to:			Davis et al. (2012)
mRS 0-2	0.029	Conditional beta distribution (α=41, β=1359)	Davis et al. (2012)
mRS 3-5	0.919	Conditional beta distribution (α=1287, β=113)	Davis et al. (2012)
Recurrent stroke	0.013	Conditional beta distribution (α=18, β=1382)	Davis et al. (2012)
Dead	0.039	Conditional beta distribution (α=55, β=1345)	Davis et al. (2012)
After year 1			Davis et al. (2012)
From independent (mRS 0-2) to:			Davis et al. (2012)
mRS 0-2	0.979	Conditional beta distribution (α=1371, β=28)	Davis et al. (2012)
mRS 3-5	0	Conditional beta distribution (α=17, β=1382)	Davis et al. (2012)
Recurrent stroke	0.013	Conditional beta distribution (α=11, β=1388)	Davis et al. (2012)
Dead	0.008	Conditional beta distribution (α=11, β=1388)	Davis et al. (2012)
From dependent (mRS 3-5) to:			Davis et al. (2012)
mRS 0-2	0	Conditional beta distribution (α=17, β=1382)	Davis et al. (2012)
mRS 3-5	0.948	Conditional beta distribution (α=1327, β=72)	Davis et al. (2012)
Recurrent stroke	0.013	Conditional beta distribution (α=54, β=1345)	Davis et al. (2012)

Dead	0.039	Conditional beta distribution (α54=, β=1345)	Davis et al. (2012)
From recurrent stroke to:			Davis et al. (2012)
mRS 0-2 (Best medical care + MT)	0.867	Conditional beta distribution (α=867, β=132)	Davis et al. (2012)
mRS 3-5 (Best medical care + MT)	0.104	Conditional beta distribution (α=103, β=896)	Davis et al. (2012)
Recurrent stroke (Best medical care + MT)	0	Conditional beta distribution (α=0, β=0)	Davis et al. (2012)
Dead (Best medical care + MT)	0.029	Conditional beta distribution (α=28, β=971)	Davis et al. (2012)
mrs 0-2 (Best medical care alone)	0.834	Conditional beta distribution (α=834, β=165)	Davis et al. (2012)
mrs 3-5 (Best medical care alone)	0.137	Conditional beta distribution (α=136, β=863)	Davis et al. (2012)
Recurrent stroke (Best medical care alone)	0	Conditional beta distribution (α=0, β=0)	Davis et al. (2012)
Dead (Best medical care alone)	0.029	Conditional beta distribution (α=28, β=971)	Davis et al. (2012)
Health utilities**			
Independent	0.74	Beta distribution (α=148, β=52)	Dorman et al. (2000)
Dependent	0.38	Beta distribution (α=76, β=124)	Dorman et al. (2000)
Recurrent	0.34	Beta distribution (α=68, β=132)	Dorman et al. (2000)
Costs ***			
Best medical care	£1,919	Gamma distribution (α=500, β=3.83)	British National Formulary (2015)
MT	£8,912	Gamma distribution (α=1000, β=8.11)	Ganesalinham et al. (2015), Davis et al. (2012)
First 3 months:			
Independent	£7,302.83	Gamma distribution (α=1000, β=7.30)	Ganesalinham et al. (2015)
Dependent	£15,627.49	Gamma distribution (α=2000, β=7.81)	Ganesalinham et al. (2015)

Fatal	£10,039.42	Gamma distribution (α=1000, β=10.03)	Ganesalingam et al. (2015)
Recurrent	£380.46	Gamma distribution (α=500, β=0.76)	Ganesalingam et al. (2015)
Ongoing per 3 months:			
Independent	£498.42	Gamma distribution (α=500, β=0.10)	Ganesalingam et al. (2015)
Dependent	£1,339.64	Gamma distribution (α=1000, β=1.34)	Ganesalingam et al. (2015)

* point estimates refer to transition probabilities, given as a proportion (0-1). ** point estimates refer to health utilities (range – 0.594, 1.000). *** point estimates refer to cost (£) in 2015/16 prices.

Incremental analysis

Cost-effectiveness was expressed as the incremental cost-effectiveness ratio (ICER) and the incremental net monetary benefit (NMB). ICERs are calculated as follows:

Incremental cost-effectiveness ratio (ICER) = ΔCosts/ΔQALY

Where ΔCosts is the difference in total costs between interventions and ΔQALY is the difference in QALYs between interventions.

The NMB is a measure of the health benefit, expressed in monetary terms, which incorporates the cost of the new strategy, the health gain obtained, and the societal willingness to pay for health gains. The NMB is calculated using the following formula:

Incremental NMB = (ΔQ*WTP) – ΔC

ΔQ = difference in QALYs: WTP = willingness-to-pay threshold (£20,000 in the UK); ΔC = difference in cost

Uncertainty

Uncertainty around the parameter estimates used in our model was fully characterised and propagated through to the model results by conducting probabilistic sensitivity analysis (PSA). This was done by defining parameter values using distributions rather than point estimates. The model was then run 5,000 times with a value randomly drawn from the assigned probability distribution. This produced a distribution of model outputs which was represented visually on the cost-effectiveness plane. Cost-effectiveness acceptability curves (CEAC) were used to represent the probability that an intervention would be cost-effective compared to the control group at a range of willingness-to-pay thresholds.

We conducted one-way sensitivity analysis on the key parameters driving the cost-effectiveness estimate of mechanical thrombectomy in our model. We tested: the cost of the mechanical thrombectomy procedure, the health utility associated with functional independence, dependence and death, the proportion of patients achieving functional independence, dependence and death, following treatment with mechanical thrombectomy or best medical care alone. We tested the impact on the model's estimate of cost-effectiveness (i.e. the ICER) of varying each of these parameters individually by +/- 20%. Further details are given in the supplementary material (Table 9).

Value of Information

Value of Information analysis on the expected value of perfect information (EVPI) was carried out to quantify the potential value of further research based on the difference between the expected NMB with perfect information and with existing information. The EVPI represents the amount a decision-maker should be willing to pay to eliminate uncertainty regarding which intervention is the best option. This uncertainty is characterised in the model in terms of parameter uncertainty and is addressed through the use of PSA which produces a distribution of outcomes, in terms of costs and QALYs, for each treatment. The difference between the NMB, based on a decision

made with perfect information (i.e. no uncertainty) and with current information, represents the EVPI. We also estimated the expected value of perfect parameter information (EVPPI). This estimates the value of reducing the uncertainty relating to specific parameters in your model. For the purpose of this analysis, we grouped together groups of related model parameters as follows; i) parameters for mRS scores at 90 days from clinical trial data; ii) utility parameters; iii) cost parameters; iv) lifetime transition parameters.

It is necessary to discount both the costs and benefits of this technology over the relevant time horizon. It has been estimated that approximately 11,000 patients with acute ischaemic stroke are eligible for mechanical thrombectomy per year in the UK (55,000 over five years) (188-190). A discount rate is therefore applied to estimate the present value of the population which may benefit over the technology's lifetime (191). For the analysis, we assumed the "effective population" (discounted population) to be 51,404 patients over a five-year period, and that the lifetime of the new technology to be five years.

Value of Implementation

We calculated the Value of Implementation as the value of perfect implementation minus the cost of implementation (45), measured over a five-year time horizon. We estimated the maximum potential Value of Implementation as the net monetary benefit of achieving 100% implementation across the UK (51,404 patients over five years). We then subtracted from this the cost of 27 comprehensive stroke centres across the UK necessary to perform this procedure. We included costs of ongoing staff salaries and initial set-up costs - such as training and equipment (full details are given in the Supplementary Material, Table 12). These costs were developed alongside two stroke clinicians working in acute ischaemic stroke. Unit costs were obtained from the literature (172) and from the Personal Social Services Research Unit (PSSRU) publication (192). Assumptions regarding the proportion of time spent on

thrombectomy and duration of training required were based on expert opinion (Keith Muir, Martin Dennis, 2018). Finally, we estimated the "break-even" level of implementation. That is, the point at which the NMB obtained from the proportion of eligible patients treated is equal to the cost of implementation.

4.6 Results

Within-trial analysis

The results of the within-trial analysis found that mechanical thrombectomy plus best medical care, compared to best medical care alone, had a total cost of £17,157 compared with £11,949. Over the course of the trial (90 days), the QALYs gained in the intervention group were 0.143, compared with 0.117 in the control group. This equates to an incremental cost of £5,207 and 0.025 QALYs associated with the addition of mechanical thrombectomy to best medical care alone and an ICER of £205,279 per QALY gained. The bootstrapped mean cost difference between groups was £5,207 (95% CI: -£1,458, £11,873) and the mean QALY difference was 0.026 (95% CI: -0.008, 0.059).

Lifetime economic model

The results of the economic model found that mechanical thrombectomy plus best medical care, compared to best medical care alone, had a total cost of £46,684 compared with £39,035 (Table 7). Over a lifetime horizon, the QALYs gained in the intervention group were 7.614, compared with 5.408 in the control group. This equates to an incremental cost of £7,649 and 2.207 QALYs associated with the addition of mechanical thrombectomy to best medical care alone and an incremental cost-effectiveness ratio of £3,466 per QALY gained and an incremental NMB of £36,484 per patient.

Table 7: Lifetime economic model results, in terms of lifetime costs and QALYs, for MT plus best medical therapy compared with best medical therapy alone (outcomes are presented per patient)

Treatment	Cost (£)	QALYs gained	Incremental cost (£)	Incremental QALYs gained	Incremental cost/QALY gained (ICER)	Incremental NMB
Best medical care	£39,035	5.408				
Best medical care + Mechanical thrombectomy	£46,684	7.614	£7,649	2.207	£3,466	£36,484

Probabilistic sensitivity analysis

The cost-effectiveness plane shows the results of running the model 5,000 times and recording the difference in cost and effectiveness between the mechanical thrombectomy and best medical care (Figure 6). Although most data points are observed in the upper right quadrant of the plane (representing the scenario of 'more costly and more effective'), there is considerable uncertainty surrounding the extent and existence of the additional expected costs and the existence and extent of the additional expected QALYs.

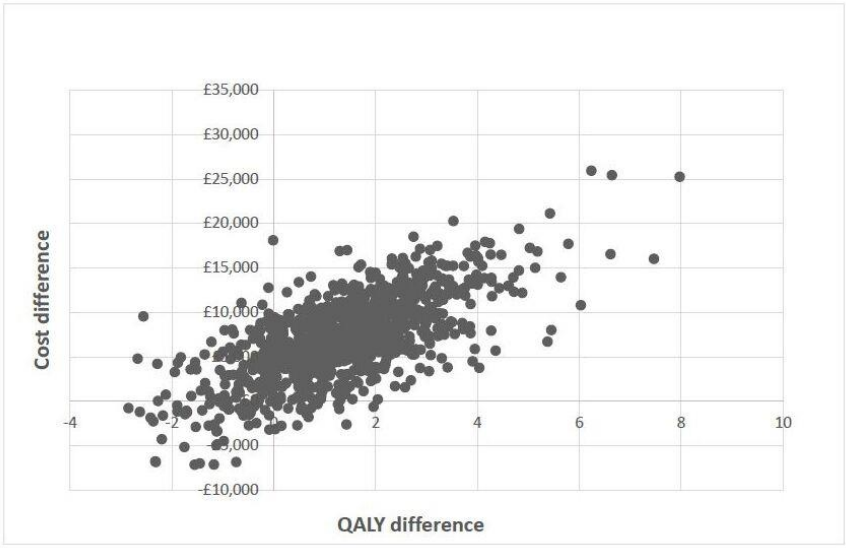


Figure 6: Probabilistic results displayed on the cost-effectiveness plane

The cost-effectiveness acceptability curve (CEAC) shows the probability of mechanical thrombectomy being cost-effective for different levels of willingness-to-pay thresholds, compared with best medical care alone (Figure 7). The CEAC shows that, at a willingness-to-pay threshold of £20,000 per QALY gained, mechanical thrombectomy has a 80% probability of being cost-effective, compared with best medical care alone.

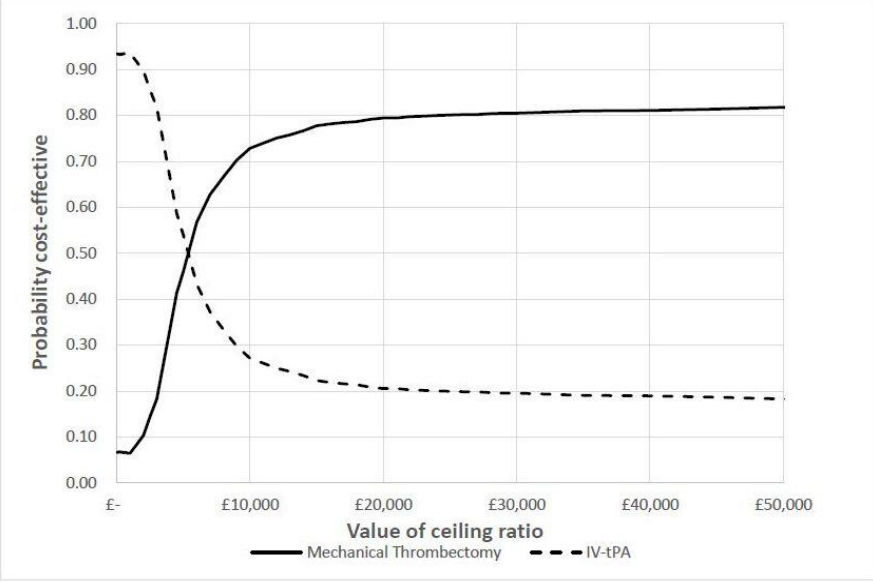


Figure 7: cost-effectiveness acceptability curve (CEAC)

One-way sensitivity analysis

We conducted one-way sensitivity analysis on the key parameters driving the cost-effectiveness estimate of mechanical thrombectomy in our model. Our results showed that varying all of these key parameters within our model had no impact on the decision problem, i.e. all ICER estimates remain below £20,000 per QALY. The parameter which had the greatest negative impact on cost-effectiveness (i.e., increased the ICER) was the proportion of patients achieving functional independence (mRS 0-2) after receiving mechanical thrombectomy.

Value of Information

The expected value of perfect information per patient affected by the decision to recommend treatment using mechanical thrombectomy is estimated at £3,178 per person. Based on our assumptions of 51,404 eligible patients over a five-year lifetime of this technology, at a willingness-to-pay of £20,000 per QALY gained, this equates to an expected value of perfect information of £163 million over a five-year period for the UK population (Figure 8).

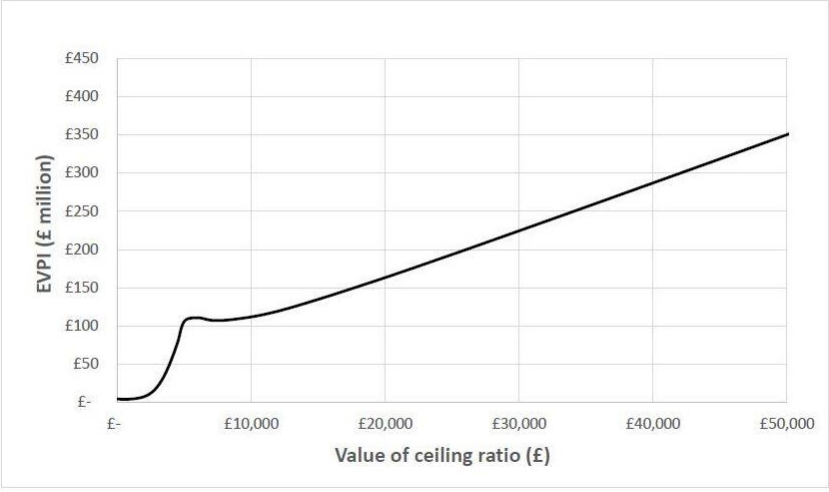


Figure 8: Expected value of perfect information for a range of willingness to pay thresholds

The expected value of perfect parameter information suggests that all of the value of reducing parameter uncertainty in our model is generated from the lifetime transition probabilities for patients following the 90-day period after stroke.

Value of Implementation

We estimate the Value of perfect Implementation as the NMB from mechanical thrombectomy (£36,484 per person) multiplied by the effective population (51,404). This implies that the expected Value of perfect Implementation in UK would be £1.7 billion. We estimate a cost of £16,404,911 per comprehensive stroke centre, over a five-year period. Hence, a total cost of £443 million to implement this procedure across the UK in 27 comprehensive stroke centres over five years (a full breakdown of the cost calculation is given in Table 8 and details of assumptions are given in supplementary material). This suggests an expected Value of Implementation of £1.3 billion over five years. We estimate the "break-even" Value of Implementation activity point at approximately 30% implementation (approx. 3,084 patients per year). Below this point, the cost of implementing mechanical thrombectomy into routine practice is expected to be greater than the benefit, in NMB terms.

Table 8: Breakdown of cost calculation for the set-up of a comprehensive stroke unit capable of performing MT, including capital costs, staff and training costs, over a five-year period

Resource	Units required	Unit cost	Set-up costs	Year 1	Year 2	Year 3	Year 4	Year 5	Resource costs per stroke unit (5 years)
Ongoing costs									
Interventional neuroradiologist (year 1)	3	£116,451	£0	£349,352					
(year 2)	3	£119,455			£358,365				
(year 3)	3	£122,537				£367,611			
(year 4)	4	£125,699					£502,794		
(year 5)	5	£128,942						£644,708	£2,222,831
Anaesthetists (year 1)	3	£17,000	£0	£51,000					-
(year 2)	3	£17,439			£52,316				-
(year 3)	3	£17,889				£53,666			-
(year 4)	4	£18,350					£73,400		-
(year 5)	4	£18,823						£75,294	£305,675
Anaesthetist assistant (year 1)	3	£6,383	£0	£19,148					-
(year 2)	3	£6,547			£19,642				-
(year 3)	3	£6,716				£20,149			-
(year 4)	4	£6,890					£27,559		-
(year 5)	4	£7,067						£28,270	£114,769
Theatre nurse (year 1)	5	£6,383	£0	£31,914					-
(year 2)	5	£6,547			£32,737				-

(year 3)	5	£6,716				£33,582			-
(year 4)	5	£6,890					£34,448		-
(year 5)	5	£7,067						£35,337	£168,019
Recovery nurse (year 1)	1	£5,153	£0	£5,153					-
(year 2)	1	£5,286			£5,286				-
(year 3)	1	£5,422				£5,422			-
(year 4)	1	£5,562					£5,562		-
(year 5)	1	£5,706						£5,706	£27,128
Radiographer (year 1)	5	£4,983	£0	£24,914					-
(year 2)	5	£5,111			£25,557				-
(year 3)	5	£5,243				£26,216			-
(year 4)	5	£5,379					£26,893		-
(year 5)	5	£5,517						£27,586	£131,166
Radiologist (year 1)	2	£23,290	£0	£46,580					-
(year 2)	2	£23,891			£47,782				-
(year 3)	2	£24,507				£49,015			-
(year 4)	2	£25,140					£50,279		-
(year 5)	2	£25,788						£51,577	£245,233
Stroke physician (year 1)	1.4	£23,290	£0	£32,606					-
(year 2)	1.4	£23,891			£33,447				-
(year 3)	1.4	£24,507				£34,310			-
(year 4)	1.4	£25,140					£35,196		-
(year 5)	1.4	£25,788						£36,104	£171,663

Ambulance transfer per MT (year 1)	1	£231	£0	£12,833					-
(year 2)	1	£237			£26,329				-
(year 3)	1	£243				£54,016			-
(year 4)	1	£249					£83,115		-
(year 5)	1	£256						£104,206	£280,499
Helicopter transfer per MT (year 1)	0.17	£2,900	£0	£27,389					-
(year 2)	0.17	£2,975			£56,191				-
(year 3)	0.17	£3,052				£115,282			-
(year 4)	0.17	£3,130					£177,384		-
(year 5)	0.17	£3,211						£222,396	£598,641
MT device costs (stent retriever, catheter, procedure pack, drapes, gowns, gloves, sheath) (year 1)	1	£4,878	£0	£271,000					-
(year 2)	1	£5,004			£555,984				-
(year 3)	1	£5,133				£1,140,656			-
(year 4)	1	£5,265					£1,755,127		-
(year 5)	1	£5,401						£2,200,501	£5,923,267
CT angiography per MT (year 1)	1	£1,200	£0	£66,667					-
(year 2)	1	£1,231			£136,773				-
(year 3)	1	£1,263				£280,604			-
(year 4)	1	£1,295					£431,766		-

(year 5)	1	£1,329						£541,329	£1,457,138
CT perfusion per MT (year 1)	1	£60	£0	£3,333					-
(year 2)	1	£62			£6,839				-
(year 3)	1	£63				£14,030			-
(year 4)	1	£65					£21,588		-
(year 5)	1	£66						£27,066	£72,857
Nurse to accompany CT scan per MT (year 1)	1	£49	£0	£2,722					-
(year 2)	1	£50			£5,585				-
(year 3)	1	£52				£11,458			-
(year 4)	1	£53					£17,630		-
(year 5)	1	£54						£22,104	£59,500
Nurse assessment per MT (year 1)	1	£4	£0	£218					-
(year 2)	1	£4			£447				-
(year 3)	1	£4				£917			-
(year 4)	1	£4					£1,410		-
(year 5)	1	£4						£1,768	£4,760
Routine nurse observation per MT (year 1)	1	£16	£0	£898					-
(year 2)	1	£17			£1,843				-
(year 3)	1	£17				£3,781			-
(year 4)	1	£17					£5,818		-
(year 5)	1	£18						£7,294	£19,635
Junior staff review per MT (year 1)	1	£13	£0	£700					-

(year 2)	1	£13			£1,436				-
(year 3)	1	£13				£2,946			-
(year 4)	1	£14					£4,534		-
(year 5)	1	£14						£5,684	£15,300
Consultant review at 24 hours per MT (year 1)	1	£35	£0	£1,944					-
(year 2)	1	£36			£3,989				-
(year 3)	1	£37				£8,184			-
(year 4)	1	£38					£12,593		-
(year 5)	1	£39						£15,789	£42,500
Training and set-up costs		£40							-
Angio suite	1	£1,800,000	£1,800,000	£160,000	£164,128	£168,363	£172,706	£177,162	£2,642,359
Interventional neuroradiologist (training)	5	£300,000	£1,500,000	£0					£1,500,000
Anaesthetists (training)	4	£35,798	£143,192	£0					£143,192
Anaesthetist assistant (training)	4	£97	£387	£0					£387
Theatre nurse (training)	5	£20,000	£100,000	£0					£100,000
Recovery nurse (training)	1	£97	£97	£0					£97
Radiologist (training for diagnostic CT)	2	£14,915	£29,830	£0					£29,830
Radiographer (training for diagnostic CT)	5	£10,937	£54,685	£0					£54,685
Stroke physician (training for diagnostic CT)	1.4	£52,700	£73,780	£0					£73,780
									-
No. of patients treated in UK				1500	3000	6000	9000	11000	-

No of patients treated per centre		56	111	222	333	407	-
Annual costs	£3,701,971	£1,108,373	£1,534,677	£2,390,209	£3,439,803	£4,229,880	-
Cost per MT		£19,951	£13,812	£10,756	£10,319	£10,382	-
					Total cost per centre over five years:		£16,404,911

4.7 Discussion

Our results indicate that mechanical thrombectomy plus best medical care, compared with best medical care alone, meets standard criteria to be considered a cost-effective use of resources in a UK health service setting. The results of our study are consistent with other UK economic evaluations which suggest the cost-effectiveness of mechanical thrombectomy over a patient's lifetime perspective (165, 172). One UK study found mechanical thrombectomy to be cost-saving. This is partly driven by the assumption of higher long-term care costs associated with disability after stroke and the savings resulting from avoidance of disability due to treatment with mechanical thrombectomy. Furthermore, the proportion of patients achieving functional independence (mRS 0-2) following mechanical thrombectomy is 60% (obtained from SWIFT-PRIME trial), compared with our estimate of 57%.

Our results suggest that the use of mechanical thrombectomy is unlikely to be cost-effective over a 90-day time horizon, based on data from the UK-based PISTE trial. This is due to a very small difference in health benefits between the two treatments observed in the trial. The incremental cost of mechanical thrombectomy over a 90-day period was £5,207, compared with £7,649 over a lifetime horizon. However, the QALY gain over a 90-day horizon was 0.025 QALYs, compared with 2.207 QALYs over a lifetime horizon. This implies that, over a lifetime horizon, there is a proportionally greater increase in QALYs than costs. The premature termination of the PISTE trial, and hence reduced sample size and some treatment crossovers, may have had an impact on the QALY difference between treatment groups. However, the estimated effect sizes were similar to those seen in other mechanical thrombectomy trials, and results were significant in the per protocol population despite small sample size. It should also be noted that best medical care in all patients in the PISTE trial included IV-tPA, in common with some other MT trials (EXTEND-IA, SWIFT-Prime), while other trials permitted inclusion of thrombolysis-ineligible patients (MR CLEAN, ESCAPE, REVASCAT). The effect of MT on very poor functional outcomes is greater among

thrombolysis-ineligible patients (193), thus PISTE may have under-estimated the proportion of highly dependent outcomes. Further, PISTE also required good baseline function, as measured by estimated pre-stroke mRS score, which may have influenced the treatment effect observed in the trial.

Our Value of Information analysis suggests that further research costing less than £163 million has the potential to be considered a cost-effective use of resources. This is because the return on the investment from further research, in terms of the costs and/or health benefits gained from choosing an alternative strategy based on the new evidence, is expected to be no higher than the figure of £163 million. The expected value of perfect parameter information suggests that all of the value of reducing parameter uncertainty in our model is generated from the lifetime transition probabilities for patients following the 90-day period after stroke. Intuitively this makes sense. The recent clinical trials have demonstrated the efficacy of mechanical thrombectomy, compared with best medical care, over a 90-day time horizon. The results of our within-trial cost-effectiveness analysis of the PISTE trial suggests that over 90-days, the benefits associated with mechanical thrombectomy do not outweigh the costs. The result is reversed over the lifetime of a patient, as the cost and utility gain resulting from reduced disability from stroke have proportionally greater influence. Hence, the finding of cost-effectiveness of mechanical thrombectomy comes from our estimates of what happens to a patient over their lifetime, i.e., it comes from our lifetime model. Further research in this area could take the form of a follow-up study aimed at identifying the mRS scores of patients following treatment with mechanical thrombectomy at future time points (i.e., 5 years, 10 years).

Our lifetime cost-effectiveness model used clinical evidence from seven RCTs of mechanical thrombectomy (using second generation stent retrievers),but did not consider subsequent trials indicating benefit from mechanical thrombectomy in

patients presenting in later time windows (6-24 hours) based on additional imaging selection criteria (188, 189). In order to estimate the cost of routinely providing mechanical thrombectomy across the UK, it was necessary to make some assumptions (see supplementary material). In terms of staffing costs, our results are likely to be an overestimate. This is because we have chosen to provide the cost of a full-time equivalent for some staff (interventional neuroradiologist) to reflect the need to have these staff available on demand over a 24-hour service focussed on delivering MT. In practice, it is likely that a proportion of these staff will spend their time on activities unrelated to thrombectomy. Support staff (e.g., anaesthetist) are assumed to spend a portion of their time supporting MT delivery, and the remaining time delivering other services. However, precise numbers required to populate a rota capable of providing a 24-hour MT service is highly uncertain and will vary by region and stroke services available. In addition, we have included the full cost of an angiography suite required to undertake the procedure to reflect the initial set-up costs required, however, in practice, this equipment will be available for other activities and hence not all costs associated with the suite will be attributable to thrombectomy.

The ability to identify patients mostly likely to benefit from mechanical thrombectomy and to triage these patients from stroke onset to initiation of treatment within the required time period presents a challenge. To meet this challenge, significant system reorganisation will be required (174). The clinical trial evidence relates to patients who were predominantly able to receive treatment within 6 hours from stroke onset, a small minority being treated beyond 6 hours in the two trials with longer time windows (ESCAPE 12 hours and REVASCAT 8 hours). Patient level meta-analysis confirms steeply declining benefit with later treatment even within the first 6 hours (194). As such, strategies aimed at minimising door-to-needle times are recommended. The role of imaging in the selection of patients for mechanical thrombectomy, as undertaken in both trials of thrombectomy beyond the 6 hour time

window (188, 189), remains uncertain for those treated within the first 6 hours, since only two trials mandated similar selection criteria (155, 156). The role of regional hospitals ("primary stroke centres"), unable to deliver mechanical thrombectomy, in the early administration of IV-tPA prior to transfer to a comprehensive stroke centre - the so called "drip and ship" model vs. the "mothership" model - is likely to require local planning dependent on service characteristics and transport networks (195). The need to maintain a minimum institutional and individual workload to maintain skills would likely pose a challenge to regional hospitals. Further research in these areas will contribute to the discussion around optimal system organisation and will impact on the cost-effectiveness of mechanical thrombectomy that will be observed in routine practice. The results of our implementation analysis suggest that the cost-effectiveness of mechanical thrombectomy in practice is not contingent on achieving full implementation. Indeed, our results suggest that any level of implementation greater than 30% is likely to be a cost-effective use of resources.

4.8 Conclusion

Based on a lifetime horizon, our economic model suggests that mechanical thrombectomy is cost-effective compared with best medical care. The CEAC showed that, at a willingness-to-pay threshold of £20,000 per QALY gained, mechanical thrombectomy has a 80% probability of being cost-effective, compared with best medical care alone. Our Value of Information analysis suggests that there is value in future research aimed at reducing the uncertainty around transitions between mRS scores in the longer term. On the assumption of full implementation being achieved throughout the UK healthcare system, we estimate that the Value of Implementation is greater than the cost of implementation. We find that this result holds for any level of implementation greater than approximately 30%.

Funding

This study was funded by the National Institute for Health and Care Research (NIHR). The NIHR has no role in the design, conduct or interpretation of the study.

Conflict of interest

The PISTE Trial Steering Committee was chaired by GAF (Stroke Association funded phase) and by H Markus (HTA phase). JF was the lay representative on the Trial Steering Committee and participated in all trial design and management decisions. The Data Monitoring Committee was chaired by K R
Lees (Stroke Association phase) and by T Robinson (HTA phase); and included S Lewis (Stroke Association phase), J Norrie (HTA phase) and A Molyneux (throughout).

Patient/public involvement

N/A

Contribution statement

RH undertook the analysis and drafted the paper. OW designed the study. KM was Principal Investigator on the PISTE trial. All co-authors reviewed and commented on the paper.

4.9 Supplementary material

Section 1: Methods and results of meta-analysis

To inform our decision tree model (first three months following stroke), we undertook a literature review of the clinical evidence relating to the treatment efficacy of both mechanical thrombectomy and IV-tPA. Treatment efficacy of IV-tPA was obtained from Goyal (2016) (HERMES collaboration). We extracted the proportion of patients entering into three possible mRS scores - mRS 0-2 (independent), mRS 3-5 (dependent), mRS 6 (dead) – following treatment with IV-tPA. Treatment efficacy of mechanical thrombectomy for the five 2015 trials was obtained from Badhiwala (2015). Badhiwala (2015) was chosen because this provided the disaggregated number of patients in each treatment group, and outcome achieved for each study, depending on treatment given. Data were extracted as the number of patients achieving each possible mRS score (0-6), depending on the treatment group to which they belonged. Treatment efficacy for THRACE and PISTE, respectively, were extracted from their original published papers. The number of patients achieving each possible mRS score (0-6) were then grouped into the number of patients achieving functional independence (mRS scores 0-2), functional dependence (mRS scores 3-5), and death (mRS scores 6).

These data were used to calculated unadjusted odds ratios for the proportion of patients achieving functional independence (Figure 9), dependence (Figure 10), and death (Figure 11) for each study. Odds ratios were calculated from the seven available trials and pooled in a meta-analysis using a fixed and random-effects model. The random-effects model was used in the base case analysis.

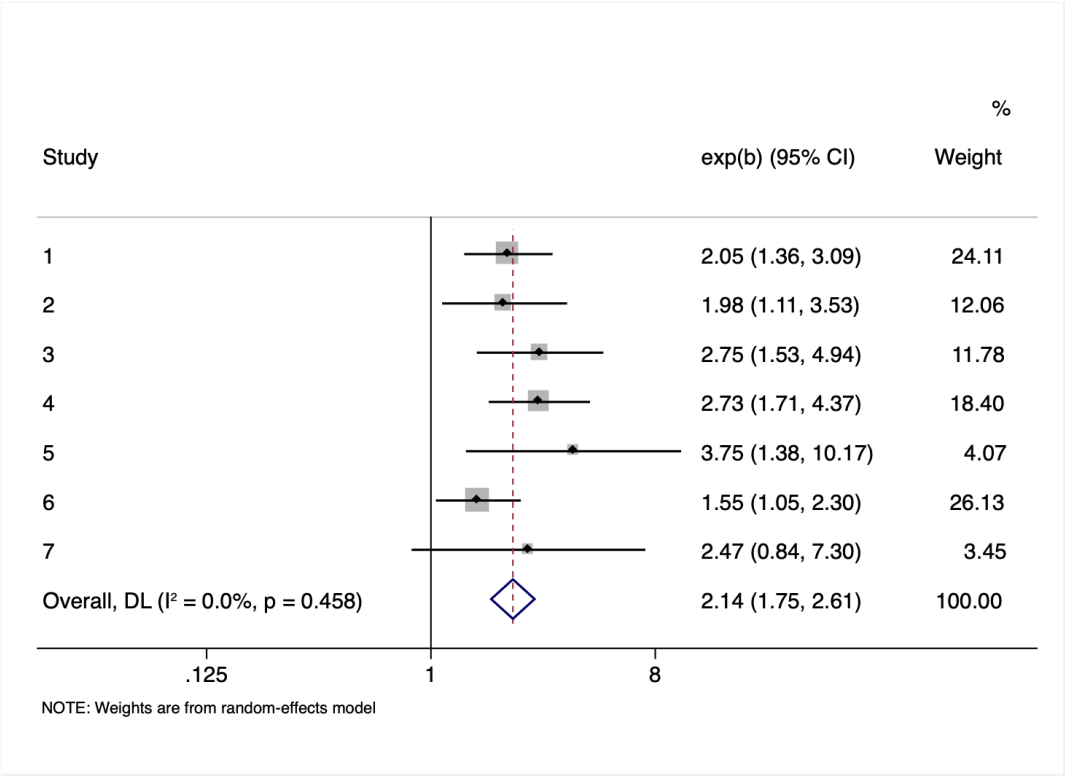


Figure 9: Forest plot of random effects meta-analysis for functional independence (mRS scores 0-2). Key for study – 1: Berkhemer et al. (2015), 2: Jovin et al. (2015), 3: Saver et al. (2015), 4: Goyal et al. (2015), 5: Campbell et al. (2015), 6: Bracard et al. (2016), 7: Muir et al. (2017).

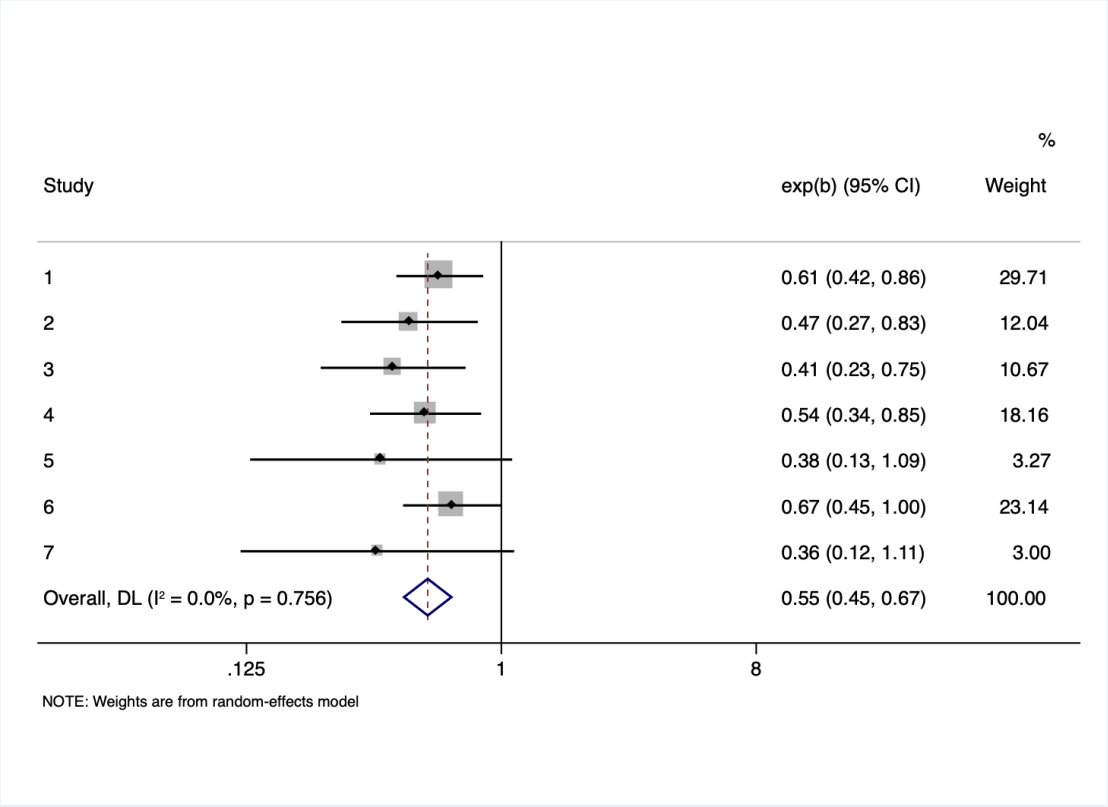


Figure 10: Forest plot of random effects meta-analysis for functional dependence (mRS scores 3-5). Key for study – 1: Berkhemer et al. (2015), 2: Jovin et al. (2015), 3: Saver et al. (2015), 4: Goyal et al. (2015), 5: Campbell et al. (2015), 6: Bracard et al. (2016), 7: Muir et al. (2017).

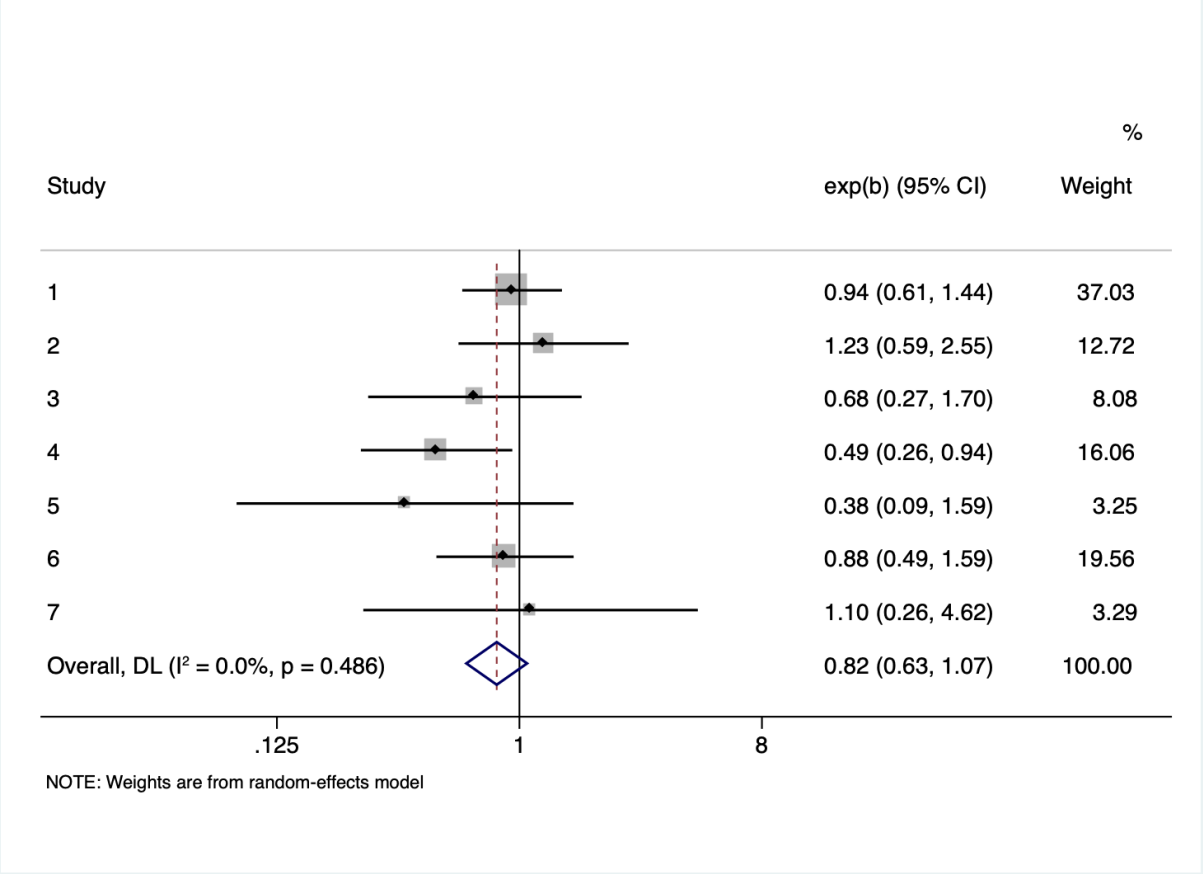


Figure 11: Forest plot of random effects meta-analysis for death (mRS score 6). Key for study – 1: Berkhemer et al. (2015), 2: Jovin et al. (2015), 3: Saver et al. (2015), 4: Goyal et al. (2015), 5: Campbell et al. (2015), 6: Bracard et al. (2016), 7: Muir et al. (2017).

Section 2: Sensitivity analysis for lifetime economic model results

Table 9 provides the base case values used in the model alongside the lower and upper bound values used in sensitivity analysis.

Table 9: Parameter estimates used in one-way sensitivity analysis

Parameter	Base case	Lower bound resource use	Upper bound resource use
Cost of mechanical thrombectomy	£8,873	£6,488	£9,733
Health utility mRS 0-2	0.74	0.69	0.79
Health utility mRS 3-5	0.38	0.29	0.47
Health utility recurrent stroke	0.34	0.27	0.41

Decision tree (MT) 0-2	0.57	0.47	0.70
Decision tree (MT) 3-5	0.27	0.21	0.33
Decision Tree (MT) 6	0.16	0.12	0.20
Decision tree (IV-tPA) 0-2	0.27	0.21	0.32
Decision tree (IV-tPA) 3-5	0.55	0.44	0.66
Decision tree (IV-tPA) 6	0.19	0.15	0.23

Figure 12 shows the results on our model's estimate of cost-effectiveness of varying key model parameters. Where possible, parameters were varied by their 95% confidence intervals. However, for some parameters, 95% confidence intervals were not available, in those cases, parameters were varied by +/- 20%. The X-axis is centred on our model's base case estimate of cost-effectiveness (ICER of £3,466).

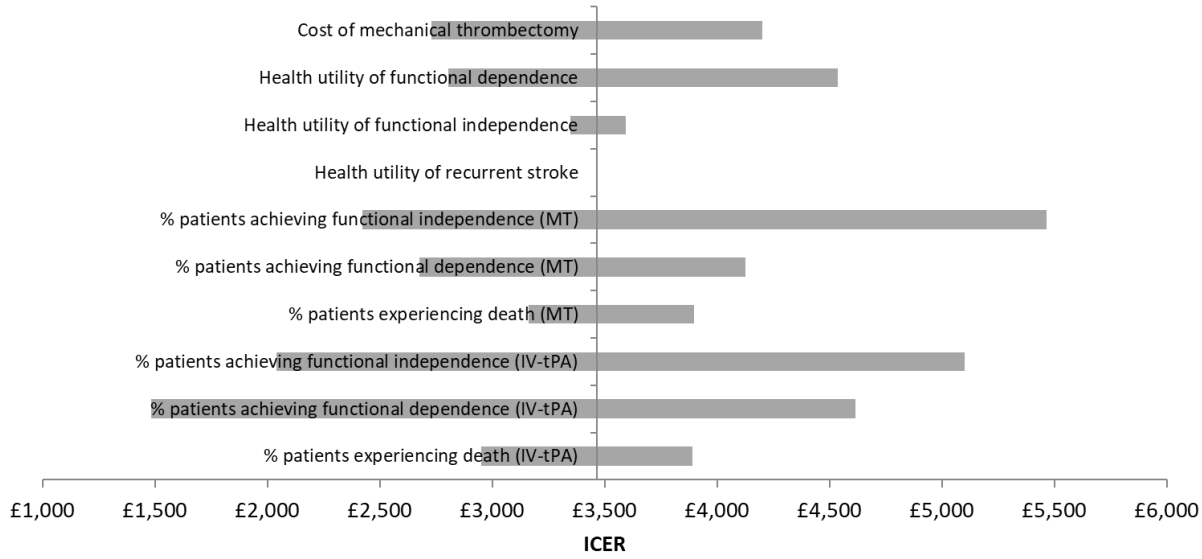


Figure 12: Results of one-way sensitivity analysis

Section 3: Cost methodology

Treatment costs (within-trial and lifetime model)

IV-tPA (alteplase)

We obtained data on IV-tPA dose per patient in the PISTE trial. The average dose of IV-tPA given to a patient in the PISTE trial was 67.9mg. The British National Formulary

provides the cost of 10mg, 20mg, and 50mg packs of IV-tPA, priced at £144, £216, and £360, respectively. Based on this, it is estimated that the average dose of IV-tPA required for a patient in the PISTE trial was £360 (50mg pack) plus £216 (20mg pack). In addition to this, staff cost estimates were obtained from Ganesalingam et al. (2015) and inflated from 2012/13 to 2014/15 prices (Table 10).

Table 10: Resource use and cost estimates for IV-tPA (alteplase)

Resource	2014/15 prices	Source
Cost of alteplase	£576.00	British National Formulary 2015
Staff time		
5 mins additional nurse time	£8.48	Ganesalingam et al. (2015)
190 mins registrar time	£288.80	Ganesalingam et al. (2015)
50 mins consultant time	£141.52	Ganesalingam et al. (2015)
5 mins routine obs by senior nurse	£2.18	Ganesalingam et al. (2015)
12 additional sets of observations at 5 mins each	£148.86	Ganesalingam et al. (2015)
5 hours 1:1 senior nurse care	£744.29	Ganesalingam et al. (2015)
10 mins overnight senior nurse care	£8.73	Ganesalingam et al. (2015)
Total cost of drug admin	£1,342.86	
Total cost of IV-tPA	£1,918.86	

Mechanical thrombectomy

The cost of mechanical thrombectomy, based on the cost of the necessary materials and staff required for the procedure, was based on estimates obtained from Ganesalingam et al. (2015). These estimates were converted from US dollar to UK pounds (at the average exchange rate for 2014 of £1:$0.64, obtained from HMRC

exchange rates). Costs were then inflated from 2013/14 to 2014/15 prices (based on an inflation rate of 0.895%, obtained from the Hospital and Community Health Services (HCHS) pay and price inflation index) (Table 11).

Table 11: Resource use and cost estimates for mechanical thrombectomy

Resource	2015 prices	Source
Cost of material		
Device	£4,885.63	Ganesalingam et al. (2015)
Guidecatheter	£103.14	Ganesalingam et al. (2015)
Guidewire	£108.57	Ganesalingam et al. (2015)
Microcatheter	£434.28	Ganesalingam et al. (2015)
Stent thrombectomy	£2,036.76	Ganesalingam et al. (2015)
Aspiration catheter	£542.85	Ganesalingam et al. (2015)
Total cost of material	£8,111.23	
Surgery staff		
Surgeon	£265.99	Ganesalingam et al. (2015)
Radiographer	£70.30	Ganesalingam et al. (2015)
Instrument nurse	£41.80	Ganesalingam et al. (2015)
Circulating nurse	£39.90	Ganesalingam et al. (2015)
Anaesthetist	£265.99	Ganesalingam et al. (2015)
Anaesthetic nurse	£77.90	Ganesalingam et al. (2015)
Total cost of surgery	£761.89	

Total cost of procedure	£8,873.12

Hospital stay (within-trial only)

The cost per day for stroke was based on figures calculated by the Scottish National Tariff and published by Information Services Division (ISD). Stroke is defined here as; intracerebral Haemorrhage (ICD10 code: I61), cerebral infarction (ICD10 code: I63) and stroke unspecified (ICD10 code: I64). Subdural and subarachnoid haemorrhage, and TIAs, are not included. The cost per day is estimated at £345. This cost was obtained from the Integrated Resource Framework (IRF) 2013/14 mapping project, 2013/14 costed file for SMR01 (Acute Inpatients & Day cases); costed using Costs Book 2013/14 SFRs 5.3 and 5.5. SMR01 data extracts as at December 2014. A UK-wide per diem cost for hospital stay for acute stroke is not provided in NHS Reference costs.

An NIHR HTA report on the cost-effectiveness of MRI in ischaemic stroke patients estimated a cost of £2,989 (2009/10 price year) per admission for ischaemic stroke with LoS 10.2 days in stroke unit, ICU and regular wards (196). This equates to approximately £293 in 2009/10 prices. Inflated to 2014/15 prices, this equates to approximately £324. This is comparable with our hospital stay cost of £345 per day.

Cost of stroke care (lifetime model only)

Costs of stroke care post-surgery were obtained from Ganesalingam (2015) and Youman (2003). These figures were based on "The Economic Burden of Stroke in the United Kingdom", Youman (2003). Although somewhat dated, Youman (2003) was described in a 2012 ScHARR study into the use of alteplase in ischaemic stroke care as follows:

"It is the opinion of the evidence review group's clinical advisors that the Youman et al. study remains the best available evidence for the cost of stroke in the UK."

Ganesalingam transformed the cost estimates calculated in Youman (2003) into costs per 3 months cycles for i) the first 3 months, broken down by mRS scores 0-2, 3-5, 6, and ii) ongoing costs every 3 months by mRS scores 0-2, 3-5.

Section 4: Within-trial cost and QALY results

The Stata output for the total cost and total QALY regressions, by trial arm, are given in Figures 13-16.

Mean total cost	Coefficient	Std. Error	P-value	95% confidence interval	
Treatment	0.362	0.218	0.098	-0.067	0.790
Age	0.094	0.317	0.768	-0.528	0.715
NIH Stroke Scale (reference group)	N/A	N/A	N/A	N/A	N/A
- Level 2	0.289	0.277	0.297	-0.254	0.833
- Level 3	0.424	0.296	0.152	-0.156	1.004
Constant	9.097	0.253	0.000	8.600	9.594

Key: Treatment (factor variable): 0=best medical care, 1=mechanical thrombectomy, Age (factor variable): 0=0-79 years, 1=80+ years, NIH Stroke Scale (categorical variable) (increasing severity): 0 (reference)=0-12, 1=13-19, 3=20+

Figure 13: Stata output for within-trial cost calculation (part 1)

Mean total cost	Margin	Std. Error	P-value	95% confidence interval	
Best medical care	11,949	1,855	0.00	8,312	15,586
Mechanical thrombectomy	17,157	2,638	0.00	11,986	22,327

Figure 14: Stata output for within-trial cost calculation (part 2)

Mean total QALYs	Coefficient	Std. Error	P-value	95% confidence interval	
Treatment	0.025	0.016	0.131	-0.007	0.058
Age	-0.063	0.025	0.012	-0.112	-0.014
NIH Stroke Scale (reference group)	N/A	N/A	N/A	N/A	N/A
- Level 2	-0.039	-1.86	0.062	-0.081	0.002

- Level 3	-0.054	-2.41	0.016	-0.099	-0.010
Baseline health utility	0.026	0.23	0.814	-0.191	0.244
Constant	0.138	1.3	0.174	-0.061	0.337

Key: Treatment (factor variable): 0=best medical care, 1=mechanical thrombectomy, Age (factor variable): 0=0-79 years, 1=80+ years, NIH Stroke Scale (categorical variable) (increasing severity): 0 (reference)=0-12, 1=13-19, 3=20+

Figure 15: Stata output for within-trial QALY calculation (part 1)

Mean total QALY	Margin	Std. Error	P-value	95% confidence interval	
Best medical care	0.117	0.012	0.000	0.094	0.141
Mechanical thrombectomy	0.143	0.012	0.000	0.119	

Figure 16: Stata output for within-trial QALY calculation (part 2)

Section 5: Value of Information analysis

The expected value of perfect information per patient affected by the decision is estimated at £3,178 per person. Based on our assumptions of 51,404 eligible patients per year over a five-year lifetime of this technology (11,000 per year, discounted over five years – health benefits are discounted in a similar manner to costs), at a willingness-to-pay of £20,000 per QALY gained, this equates to an expected value of perfect information of £163 million over a ten-year period for the UK population. We also ran the VoI analysis using groups of related parameters (costs, utilities, transition probabilities over 90 days from the trial data, and lifetime transition probabilities from the literature). A graphically representation of the respective contribution to the Value of Information from each parameter group is given in Figure 17.

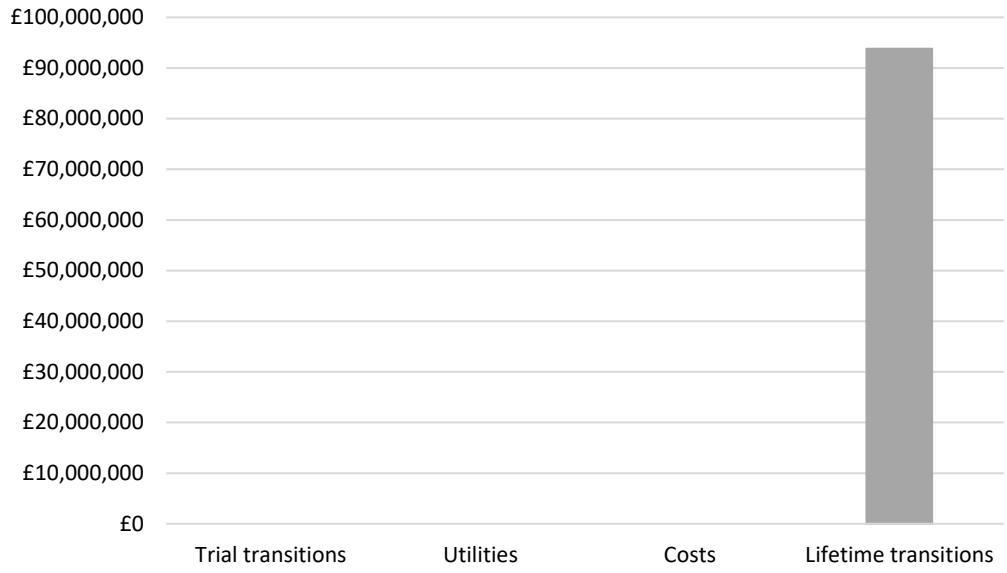


Figure 17: EVPPI for UK over 10 years (£), by parameter groups

This analysis suggests that all of the value of further research comes from the uncertainty relating to lifetime transition probabilities of patients following the 90-day trial period studied in the clinical trials. These probabilities are reported in Davis (2012), which were derived from the Lothian Stroke Register. It is the variation of the parameter estimates around the 95% CIs of the lifetime transition probabilities that have the potential to reverse the overall result from cost-effective to not cost-effective, and hence this is where the value of further research resides. However, we note that other estimates of uncertainty, such as +/- 20% of the point estimate, or estimates based on expert elicitation, may have lead to alternative values for the total EVPPI. In addition, VoI methods only capture uncertainty related to parameter uncertainty in a model, and do not account for other sources of uncertainty, such as structural uncertainty, which may impact on the value of further research.

Section 6: Value of Implementation analysis

This section details the additional costs associated with implementation incorporated in the Value of Implementation analysis, alongside the required assumptions. The assumptions were obtained from expert elicitation of two stroke clinicians working in

acute stroke care (Keith Muir, Martin Dennis, 2018). Details of each cost item are given in Table 12.

1. We assume that a stroke centre does not begin on day 1 by operating at full capacity, but rather there is increase over time in patient number and staff number required to treat them. The figures reached at year 5 is what we assume would be a stroke centre working at full capacity.

2. For some staff, only a proportion of their time was assumed to be related to mechanical thrombectomy. This includes anaesthetics, anaesthetic assistants, theatre nurse, recovery nurse, radiographer, and stroke physician stroke. For these staff, it was assumed that 20% of their time was related to mechanical thrombectomy.

3. The use of helicopter transfer with vary significantly geographically (i.e. patient distance from stroke centre). UK government statistics suggest that 0.17% of the UK population live in a rural setting. We have therefore assumed as our base case that anyone living in a rural setting would require helicopter transfer.

4. We assume that for anaesthetics and anaesthetic assistants, there are no significant new skills to acquire in order to delivery mechanical thrombectomy, and hence that these skills could be covered in a one-day training course. We have estimated their cost of training based on the average annual salary for these roles divided by 330 to get the cost of one day of missed work (the number of days in the year, minus holidays).

5. To estimate the cost of training an interventional neuroradiologist, we have assumed the individual would require 6 years of training (4 years, plus 2 years interventional fellowship). We have not assumed that current staff could simply

undertake the 2-year fellowship as this would lead to a displacement of staff elsewhere in the system.

Table 12: Costs of implementation included in budget impact analysis

Staff	
Interventional neuroradiologist	
Assumption	Full-time salary cost. Equivalent to medical consultant, PSSRU 2015.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Anaesthetists	
Assumption	20% of their time related to thrombectomy. Equivalent to medical consultant, PSSRU 2015.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Anaesthetist assistant	
Assumption	20% of their time related to thrombectomy. Band six hospital nurse. PSSRU 2015.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Theatre nurse	
Assumption	20% of their time related to thrombectomy. Band six hospital nurse. PSSRU 2015.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Recovery nurse	
Assumption	20% of their time related to thrombectomy. Band five hospital nurse. PSSRU 2015.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Radiographer	
Assumption	20% of their time related to thrombectomy. Hospital radiographer. PSSRU 2015.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Radiologist	
Assumption	Full-time salary cost. Equivalent to medical consultant, PSSRU 2015.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)

Stroke physician	
Assumption	Full-time salary cost. Equivalent to medical consultant, PSSRU 2015.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Ambulance transfer	
Assumption	One ambulance transfer per thrombectomy. PSSRU 2015.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Helicopter transfer	
Assumption	17% of thrombectomies requiring helicopter transfer, based on proportion of UK living in rural area. Cost from Great North Air Ambulance Service.
Source	17% figure is based on UK Government Statistics. Available at https://www.gov.uk/government/publications/rural-population-and-migration/rural-population-201415
MT device costs (stent retriever, catheter, procedure pack, drapes/gowns/gloves/sheath)	
Assumption	Cost per procedure.
Source	Lobotesis et al. (2016). J Med Econ. 2016 Aug;19(8):785-94. doi: 10.1080/13696998.2016.1174868
CT angiography per MT	
Assumption	Cost per procedure.
Source	Lobotesis et al. (2016). J Med Econ. 2016 Aug;19(8):785-94. doi: 10.1080/13696998.2016.1174868
CT perfusion per MT	
Assumption	Cost per procedure.
Source	Lobotesis et al. (2016). J Med Econ. 2016 Aug;19(8):785-94. doi: 10.1080/13696998.2016.1174868
Nurse to accompany CT scan per MT	
Assumption	Cost per procedure.

Source	Lobotesis et al. (2016). J Med Econ. 2016 Aug;19(8):785-94. doi: 10.1080/13696998.2016.1174868
Nurse assessment per MT	
Assumption	Cost per procedure.
Source	Lobotesis et al. (2016). J Med Econ. 2016 Aug;19(8):785-94. doi: 10.1080/13696998.2016.1174868
Routine nurse observation per MT	
Assumption	Cost per procedure.
Source	Lobotesis et al. (2016). J Med Econ. 2016 Aug;19(8):785-94. doi: 10.1080/13696998.2016.1174868
Junior staff review per MT	
Assumption	Cost per procedure.
Source	Lobotesis et al. (2016). J Med Econ. 2016 Aug;19(8):785-94. doi: 10.1080/13696998.2016.1174868
Consultant review at 24 hours per MT	
Assumption	Cost per procedure.
Source	Lobotesis et al. (2016). J Med Econ. 2016 Aug;19(8):785-94. doi: 10.1080/13696998.2016.1174868
Training	
Interventional neuroradiologist	
Assumption	Six years of training required. Based on a salary of £50,000 per year.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Anaesthetists	
Assumption	Three months of training required. Based on an hourly rate of £53.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Anaesthetist assistant	
Assumption	One day of training required. Cost equivalent to a single day assuming an annual salary of £32,000.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)

Theatre nurse	
Assumption	One month of training required. Based on an hourly rate of £32.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Recovery nurse	
Assumption	One day of training required. Cost equivalent to a single day assuming an annual salary of £32,000.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Radiologist (training for diagnostic CT)	
Assumption	Six weeks of training required. Based on an hourly rate of £44
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Radiographer (training for diagnostic CT)	
Assumption	6 weeks of training required. Based on a total cost of training programme of £10,000.
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Stroke physician (training for diagnostic CT)	
Assumption	Six weeks of training required. Based on an annual salary of £52,700
Source	Expert opinion (Keith Muir, Martin Dennis, 2018)
Equipment	
Bi-plane angiography suite	
Assumption	Cost of a single bi-plane angiography suite in year 1, plus maintenance costs in years 2-5 (estimated at 2.5% of total value of suite per year).
Source	Report on "Health technology assessment of a national emergency endovascular service for mechanical thrombectomy in the management of acute ischaemic stroke". Produced by the Health Information and Quality Authority, Republic of Ireland (2017). Accessed on 10th May 2023. Available at https://www.hiqa.ie/sites/default/files/2017-02/Mechanical-Thrombectomy-technical-report.pdf

Chapter 5: Central venous access devices for the delivery of systemic anticancer therapy: an economic evaluation.

5.1 Foreword

I began my involvement in the Central Venous Access Devices for the Delivery of Systemic Anticancer Therapy (CAVA) trial in 2018. I led the economic evaluation of the trial, adopting a cost-utility (cost-per-QALY gained) approach, as recommended by the National Institute for Health and Care Excellence (NICE) guide for technology appraisal (2014). Our analysis found that the mean total patient cost on a PORT was greater than on a PICC, and comparable with a HICK. Adjusted for catheter dwell time (time on device), the total mean cost per catheter week per patient was lower on a PORT compared with both PICC and HICK. However, there was no meaningful difference in QALYs gained across devices. The lack of any meaningful difference in quality of life suggested by the QALY measure was in contrast to the strong preference for PORT identified in both the qualitative research conducted within the CAVA trial and previously published research (197-199).

Complex interventions are typically the reserve of population level public health studies. However, interventions in a clinical setting can also be complex. This is particularly relevant in the design and evaluation of medical devices. In the case of a venous access device for the delivery of anti-cancer therapy, health-related quality of life, as recorded by the EQ-5D instrument, may be dominated by factors unrelated to venous access device received – such as disease severity and treatment-related toxicity. In this context, the use of a cost-per-QALY framework may be limited in its ability to capture the value of a medical device. For this reason, I chose to undertake a cost-consequence analysis. This approach allowed us to disaggregate a range of clinical and cost outcomes relevant to patients and decision-makers.

Given the variation in provision and delivery of venous access devices for anti-cancer therapy throughout the UK, it is important to consider how a PORT service could be implemented in routine practice. At present, few oncology centres in the UK offer a PORT service through the NHS. Those centres which do offer a service are typically "radiology-led" – that is, the procedure is undertaken by an interventional radiologist, with support staff, in a theatre setting. However, a fully "nurse-led" service is available at The Christie NHS Foundation Trust in Manchester - the largest single site cancer centre in Europe. In 2020 I visited The Christie to interview the head nurse responsible for implementing a nurse-led PORT service to understand how and why this service was introduced. The viability of fully nurse-led service has important implications for the potential cost-effectiveness of a PORT service in routine clinical practice. For this reason, I chose to supplement our analysis of the CAVA trial with a Value of Implementation analysis, based on a plausible service delivery configuration developed alongside specialist oncology nurses and intervention radiologists working in this area.

5.2 Title, authorship, and publication details

Heggie, R., Jaiswal, N., McCartney, E., Moss, J., Menne, T., Jones, B., Boyd, K., Soulis, E., Hawkins, N., Wu, O. (2021) Central venous access devices for the delivery of systemic anticancer therapy: an economic evaluation.

This article is under review with the journal Value in Health.

The overall work has been led by me and I take full responsibility for it. In this chapter, I use the terms 'we' and 'our' to recognise the contribution of all authors.

Central venous access devices for the delivery of systemic anticancer therapy: an economic evaluation

Robert Heggie, MSc, Research Associate[1], Nishant Jaiswal, PhD, Research Associate [1], Elaine McCartney, MSc, Biostatistician[1,2], Jon Moss, MBChB, Professor[1], Tobias Menne, MBChB, Haematologist[3], Brian Jones, MBChB, Honorary Professor[4], Kathleen Boyd, PhD, Reader[1], Eileen Soulis, MSc, Project Manager[2], Neil Hawkins, PhD, Professor[1], Olivia Wu, PhD, William R Lindsay Chair of Health Economics[1].

[1] Health Economics and Health Technology Assessment (HEHTA), School of Health and Wellbeing, University of Glasgow, G12 8RZ, United Kingdom.
[2] Cancer Research UK, Clinical Trials Unit, Beatson Cancer Centre, Great Western Road, Glasgow, G12 0YN, United Kingdom.
[3] Haematology Department, Northern Centre for Cancer Care, The Newcastle upon Tyne Hospitals, Newcastle, NE7 7DN, United Kingdom.
[4] School of Infection and Immunity, University of Glasgow, G12 8TA United Kingdom.

Corresponding author: Robert Heggie, Health Economics and Health Technology Assessment (HEHTA), School of Health and Wellbeing University of Glasgow, 1 Lilybank Gardens, Glasgow, G12 8RZ, United Kingdom. Email: robert.heggie@glasgow.ac.uk

Funding: this work was supported by the National Institute of Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme. Award number 11/67/01.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation,

review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of interest statement: there are no conflicts of interest to report.

Acknowledgement: none reported.

Author contributions: conceptualisation: RH, OW, KB, NH, data curation: EM, ES, formal analysis: RH, funding acquisition: OW, JM, investigation: JM, TM, BJ, methodology: RH, NJ, OW, NH, project administration: RH, resources: JM, TM, BJ, software: RH, NJ, supervision: OW, validation: NJ, visualisation: RH, OW, KB, writing – original draft: RH, writing– review & editing: RH, NJ, EM, JM, TM, BJ, KB, ES, NH, OW

5.3 Abstract

Objectives

Patients undergoing long-term anti-cancer therapy typically require one of three venous access devices (VADs): HICK, PICC, or PORT. Recent evidence has shown PORT is safer and improves patient satisfaction. However, PORT did not show improvement in quality-adjusted life years (QALYs) and was more expensive. Decisions regarding cost-effectiveness in the UK are typically informed by a cost-per-QALY metric. However, this approach can be limited in its ability to capture the full range of relevant outcomes, especially in the context of medical devices.

Methods

Cost-consequence analysis comparing HICK, PICC and PORT to disaggregate the following clinical and economic outcomes: complication, infection, non-infection, chemotherapy interruption, unplanned device removals, health utilities, device insertion cost, follow-up cost, and total cost. We conducted Value of Implementation analysis to estimate the value of introducing PORT service into practice within the NHS.

Results

PORT was superior in terms of overall complication rate, compared with both HICK (0.422 (0.286 to 0.622)) and PICC (0.295 (0.189 to 0.458)) and less likely to lead to an unplanned device removal. There was no meaningful difference in the number of days of chemotherapy interruption or health utilities. Total cost with device in situ was lower on PORT, compared with Hickman (£-98.86 (-189.20 to -8.53)) and comparable with PICC (-£48.57 (-164.99 to 67.86)). The value to the NHS of a PORT service may be up to £27m.

Conclusion

Our findings suggest that PORT is both safe and cost-effective. Decision-makers should consider introducing PORT into routine practice in the NHS.

Highlights

Several clinical trials have demonstrated that PORT is associated with fewer complications, compared with HICK or PICC devices. A recent study found that the total cost of PORT was greater than PICC and similar to HICK. However, accounting for catheter dwell time, the cost per catheter week was lower for PORT. While there was no meaningful difference in QALYs gained using PORT, several qualitative studies have suggested a preference for PORT among patients.

Cost-effectiveness in the UK is typically assessed using the cost-per-QALY framework. However, in the context of a complex intervention, such as a medical device, the cost-per-QALY framework is not always appropriate. This is because complex interventions may impact on a range of outcomes relevant to patients and decision-makers. Furthermore, when considering complex interventions, implementation is key – that is, where and how an intervention will be implemented in routine practice.

In this study a cost-consequence analysis was employed to disaggregate a range of clinical and economic outcomes associated with the choice of venous access device. We found that PORT is superior to both HICK and PICC, for the majority of outcomes we measured – most importantly, for safety and cost. In addition, a Value of Implementation analysis found that PORT was likely to be considered cost-effective in routine practice within the NHS.

5.4 Introduction

Patients who undergo long-term anti-cancer therapy typically require one of three venous access devices (VADs): subcutaneously tunnelled central catheters (Hickman-type device; HICK), peripheral inserted central catheters (PICC) or implantable chest wall port (PORT). Evidence-based guidance for the use of VADs in long-term anti-cancer therapy is lacking. HICK has traditionally been the most commonly used device. However, the ease of insertion and perception that HICK and PICC were comparable in terms of safety, meant that the use of PICC has come to dominate in recent years. While PORT has been available for several decades, a lack of evidence on the cost-effectiveness of PORT, and how such a service would be delivered, are possible reasons why the use of PORT has remained minimal in the UK.

Previous research has found that PORT was associated with fewer complications compared with both HICK (200) and PICC (201). Despite the greater initial insertion cost associated with a PORT, the reduced rate of complications led to a lower cost compared with HICK (197) and PICC devices (202). However, another study found no difference in cost, despite the lower rate of complications on a PORT (198). Most recently, the CAVA trial found that HICK and PICC were comparable in terms of overall complications, and that PORT was superior to both HICK and PICC (203). A cost-utility analysis alongside the CAVA trial compared the costs and quality-adjusted life-years (QALYs) associated with the use of each device (204). PORT was associated with a small, non-statistically significant, difference in cost (-£45) and QALYs (0.004) compared with Hickman and a large difference in cost (£1,665), but small, non-statistically significant, difference in QALYs (-0.018) compared with PICC.

However, qualitative research suggests that PORT is associated with benefits not captured within the QALY measurement (197-199). Using a device-specific questionnaire, Patel et al. (2014) found that while there was no measured difference in quality of life between PORT and PICC, patients reported that there were aspects of

quality of life not captured within the study's questionnaire (198). In particular, the ability to shower, bath and swim while using a PORT. A significant benefit in favour of PORT was observed using a device-specific questionnaire in the CAVA study (204). A qualitative analysis involving 42 patients over eight focus groups identified a pattern of device preferences that favoured PORT (199). In particular, PORT was perceived to offer unique psychological benefits, including a greater sense of freedom and the ability to "forget" about their treatment.

Decisions regarding the cost-effectiveness of health technologies are typically informed by a cost-utility (cost-per-QALY) analysis, as recommended by the National Institute for Health and Care Excellence (NICE) guidance for technology appraisal. Because QALYs are not disease specific, the cost-per-QALY approach can be used to compare the net benefit of a health technology across diseases areas. This makes the cost-per-QALY framework extremely valuable for decision making. However, this approach is not always sufficient for the evaluation of complex interventions, such as medical devices. This is because the introduction of a complex intervention may impact on a range of clinical and economic outcomes which are not captured within the cost-per-QALY framework. Given the challenges of capturing the impact of a VAD within the cost-per QALY framework, previous findings on the relative cost-effectiveness of HICK, PICC or PORT may have been limited. Furthermore, there is currently a lack of clarity in terms of how VADs should be delivered in routine practice (205). HICK and PORT are typically delivered in a theatre setting, whereas PICC can be delivered at the bedside. Therefore, limited access to a theatre setting means that the use of PICC may be based on necessity rather than evidence-based practice. Uncertainty regarding cost-effectiveness and the appropriate service model of PORT may explain why implementation has hitherto been less than expected. The aim of this study was to estimate the cost-effectiveness of HICK, PICC and PORT devices in routine clinical practice, using data from the CAVA trial.

5.5 Methods

We undertook an economic evaluation from the perspective of the UK NHS, using a cost-consequence approach to disaggregate a range of clinical and economic outcomes that are relevant to patients and decision-makers. We used data from the CAVA trial which compared the clinical effectiveness of these three devices (203). Not all VADs were available at each site within the CAVA trial. Some sites randomised participants to all three VAD options, while some sites only randomised between two possible VADs. Therefore, an individual participant (IPD) network meta-analysis (NMA) was used to estimate clinical and economic outcomes from the four possible randomisation options of the CAVA trial. In addition, we used a Value of Implementation analysis to estimate the cost-effectiveness of introducing a PORT service into routine clinical practice, based on a plausible implementation strategy.

Perspective, discount rate and time horizon

The cost-consequence analysis was undertaken from the perspective of the UK National Health Service (NHS) and personal social services (PSS) over a one-year time horizon (33). The analysis was based on the intention-to-treat population (1,061 patients) from the CAVA trial. The Value of Implementation analysis evaluated the costs and benefits associated with the implementation of a PORT service over a five-year time-period. We assumed that 1,000 patients would require a VAD at a single oncology site per year. This equates to an "effective population" (discounted population) of 4,673 patients over five years. The population was discounted at 3.5%.

Clinical and economic outcomes

We estimated nine outcomes of interest to patients and decision-makers – six clinical outcomes and three economic outcomes (Table 13). The CAVA trial captured resource use relating to device insertion and follow-up visits. The resource use associated with device insertion included both staffing and setting requirements, alongside the cost of the VAD itself. Follow-up visits included both unplanned inpatient and outpatient

visits during the follow-up period. Unit costs were attached to all resource use items and costs were presented for the price year 2017/18. Full details of the clinical and economic outcomes and methodology is available elsewhere (204).

Table 13: Summary measures included, definition, data format, estimation procedure, and summary statistic obtained

	Definition	Data format	Estimation procedure	Summary statistic
Clinical outcomes				
Complication	Composite of infection (suspected or confirmed) or mechanical failure	Count	Negative binomial regression	Difference in mean rate
Infection	Composite of laboratory-confirmed blood stream infection, possible catheter-related blood stream infection, exit site infection.	Count	Negative binomial regression	Difference in mean rate
Non-infection complication	Composite of inability to aspirate blood, venous thrombosis related to device, pulmonary embolus related to device, mechanical failure, other complications.	Count	Negative binomial regression	Difference in mean rate
Days of chemotherapy interruption	Number of days of chemotherapy interruption during the trial period.	Count	Negative binomial regression	Difference in mean rate
Unplanned device removal	Device removal due to complications, patient preference, or other reasons.	Binary (yes/no)	Logistic regression	Difference in odds ratio
Health utilities	Health related quality of life measured using the EQ-5D-3L questionnaire.	Continuous	Mixed-effects regression	Difference in mean
Costs				
Device insertion cost	Cost of device and cost of staff and setting required for insertion.	Continuous	GLM regression	Difference in mean (total)
Follow-up costs (Inpatient + outpatient) per catheter week	Unplanned inpatient and outpatient visits during the follow-up period.	Continuous	Two-part model (logit and GLM)	Difference in mean (per catheter week)
Total cost per catheter week	Device insertion cost plus follow-up costs.	Continuous	GLM regression	Difference in mean (per catheter week)

Individual patient data network meta-analysis

The CAVA trial recruited participants via four randomisation options. Therefore, each randomisation option was treated as a separate sub-study in the analysis. We used a two-stage multivariate random effects model to perform the individual participant data network meta-analysis (206). In the first stage, we used the individual participant data to estimate summary measures for each study for each outcome of interest. Final estimates combined in NMA were based on the difference in effect between a device and a reference device (HICK).

The mean difference in the log rate for all count outcomes (complication, infection, non-infection complication, number of days of chemotherapy interruption) was estimated using a negative binomial regression. We adjusted for the time of device in situ for each patient. Results were exponentiated and presented as difference in mean rate.

To estimate the odds of an unplanned device removal we created two groups – planned device removal and unplanned device removal – based on the reasons for device removal data obtained from the CAVA trial. Within the planned removal group were the following reasons: planned removal/end of treatment, and patient deceased. Within the unplanned device removal were the following reasons: removal for complications, removal due to patient preference, removal for other reason. We used logistic regression to estimate the odds of being in the unplanned device removal group, based on device received. A full breakdown of the number of patients in each group in given is Supplementary Material, Figures 28-30.

The difference in mean health utilities was estimated using a mixed-effects linear regression, accounting for the repeated measure of patients' health utility over the trial period.

The mean device insertion cost for each device was estimated using a generalised linear model (GLM). Follow-up costs per catheter week consisted of inpatient and outpatient costs during the follow-up period, divided by the dwell time (in weeks) on device. As there were patients with no follow-up costs, we used a logit regression to estimate the proportion of patients with zero costs, and GLM with log link and gamma family to estimate mean follow-up costs, conditional on the patient having a positive follow-up cost. The mean total patient cost (combination of device insertion and follow-up cost) per catheter week over the trial period was estimated using a GLM, with log link and gamma family.

We adjusted our regression models for the trial stratification factors: BMI, device history, site of enrolment. The stratification factors were defined as follows: BMI was dichotomised into <30mg/kg^2 and ≥30mg/kg^2; device history was categorised as "any history" or "no history", and site of enrolment retained the six sites with the highest recruitment and combined the smaller sites into one "other" site.

The results of the NMA are presented as a cost-consequence analysis (Table 13). We used a "traffic light system" to demonstrate where a device was statistically significantly superior (green) to the reference device, no different (amber), or statistically significantly inferior (red). We also ranked each device according to the surface under the cumulative ranking (SUCRA) curve method for each outcome of interest (207).

Value of Implementation analysis

We used the Value of Implementation framework to estimate the value to the NHS of implementing PORT into routine practice (4). This approach involves using an estimate of the net benefit – expressed in monetary terms. This is then scaled up to the eligible population level to estimate the population net benefit. We then subtract from this

the cost of implementation. If the population net benefit is greater than the cost of implementation, then implementation would be considered cost-effective.

A reduction in the rate of complications associated with a PORT, compared with HICK and PICC is a clear benefit of PORT. Among potential complications associated with a PORT, infection is a common and potentially serious complication. For this reason, we chose the difference in rate of infection associated with a PORT, compared with HICK and PICC, as the measure of benefit in the Value of Implementation calculation.

To expressed the benefit of a PORT (in terms of reduced infection) in monetary terms, we estimated a willingness to pay value to avoid an infection of £16,095. This is an approximate cost for treating a patient for coagulase negative staphylococci (CNS) (a common infection associated with VADs) for upto 14 days in an oncology ward using intravenous vancomycin. These assumptions were based on expert elicitation with a microbiologist (Brian Jones, 2023) involved in the CAVA trial and clinicial guidelines (208).

To determine the Value of Implementation in routine clinical practice, we also needed to incorporate additional costs which were not captured within the CAVA trial. Based on expert opinion [interviews with clinicians and stakeholders at The Beatson Institute for Cancer Research (Jon Moss, Ram Kasthuri, 2022) and The Christie NHS Foundation Trust (Steve Hill, 2020)), we developed a plausible scenario for the delivery of a PORT service. In our scenario, we assume 1,000 patients would require a venous access device at a single oncology site per year. While on treatment, patients would require regular device maintenance (e.g., flushing) (209), device replacement if necessary, and device removal at treatment completion. In the first year of implementation, staff would incur additional training costs. Full details of the assumptions made in the base case analysis and uncertainty analysis are given in Supplementary Material.

Based on a plausible scenario for the delivery of PORT, we evaluated the following scenarios relating to implementation of a PORT service:

1) What is the value of achieving 100% and 50% implementation?
2) What level of implementation do we require for the benefits to exceed the cost?
3) If we assume full implementation can be achieved, what is the maximum implementation cost allowable for benefits to exceed costs?
4) If we want to be able to offer a PORT to 50% of patients, what is the maximum implementation cost allowable for benefits to exceed costs?
5) What is the minimum willingness to pay threshold for infections avoided that would be required for PORT to be cost-effective in practice?

5.6 Results

Results of individual participant data network meta-analysis

PORT was ranked as the best choice of device for seven out of the nine outcomes measured in this analysis (Table 14). PICC was ranked best for two outcomes – device insertion cost and health utilities. However, the magnitude of effect and confidence intervals shows that there was little difference in health utilities among devices. HICK did not rank best for any outcomes.

In terms of the rate of overall complications, PORT was superior to both HICK and PICC. This was primarily driven by the benefit of PORT in relation to non-infection complications. While PORT was superior to HICK in terms of infection rate, there was no statistically significant difference in infection rate between PORT and PICC. PORT was superior to both HICK and PICC in terms of the odds of an unplanned device removal. There was no meaningful difference among devices for both days of chemotherapy interruption and follow-up costs. While the initial device insertion was more expensive for PORT compared with either HICK or PICC, the total cost with

device in situ was significantly less on PORT, compared with HICK and comparable with PICC.

Table 14: Results of network meta-analysis for each outcome of interest

	Surface under the cumulative ranking curve (SUCRA)	PICC V HICK*	Port V HICK*	Port V PICC*
Complication rate	Best: Port Worst: PICC	1.433 (0.234, 1.973)	0.422 (0.286, 0.622)	0.295 (0.189, 0.458)
Infection complication rate	Best: Port Worst: HICK	0.412 (0.258, 0.661)	0.307 (0.199, 0.473)	0.744 (0.419, 1.320)
Non-infection complication rate	Best: Port Worst: PICC	2.590 (1.425, 4.706)	0.510 (0.271, 0.958)	0.197 (0.103, 0.378)
Days of chemotherapy interruption	Best: Port Worst: HICK	0.262 (0.056, 1.225)	0.212 (0.042, 1.062)	0.809 (0.154, 4.256)
Unplanned device removal	Best: Port Worst: HICK	1.076 (0.988, 1.171)	0.828 (0.767, 0.893)	0.769 (0.702, 0.843)
Health utilities	Best: PICC Worst: Port	0.006 (-0.021, 0.033)	-0.007 (-0.034, 0.020)	-0.013 (-0.040, 0.014)
Device insertion cost (total)	Best: PICC Worst: Port	£-604.68 (-643.83, -565.54)	£368.12 (323.88, 412.36)	972.80 (917.83, 1027.78)
Follow-up costs (inpatient + outpatient) (per catheter week)	Best: Port Worst: HICK	£-55.16 (-201.33, 91.00)	£-105.14 (-242.20, 31.93)	-49.98 (-159.28, 59.33)
Total cost (per catheter week)	Best: Port Worst: HICK	£-50.30 (-181.31, 80.72)	£-98.86 (-189.20, -8.53)	-48.57 (-164.99, 67.86)

Key – green: new device is statistically significantly better than the reference device. Amber: there is no statistically significant difference between devices. Red: new device is statistically significantly worse than the reference device.
*Reference device

Value of Implementation

The value to the NHS of full implementation (i.e., 100% of patients receiving a PORT), compared with HICK and PICC, respectively, is approximately £24m and £800,000 (Scenario 1, Table 15). That is, if we achieve full implementation, the monetary value we obtain from infections avoided, is greater than the cost of setting up a PORT service. If PORT is received by 50% of patients, the Value of Implementation for PORT is approximately £12m compared with HICK, and £400,000 compared with PICC.

Any level of implementation (i.e., uptake greater than zero) of a PORT service is likely to be cost-effective, compared with both HICK and PICC (scenario 2, Table 15). This is due to the value of the infections avoided, compared with the relatively low implementation (set-up) costs and per patient treatment (variable) cost. Implementation cost of a PORT service could be as high as £24m, compared with HICK, and £800,000 compared with PICC, and still be considered cost-effective (Scenario 3, Table 15).

If PORT is offered to 50% of patients requiring a VAD, the maximum cost of implementation for which PORT would still be considered cost-effective is £12m compared with HICK, and £400,000 compared with PICC (Scenario 4, Table 15).

At a level of £0 willingness to pay for infections avoided, the value of PORT implementation is £5m compared with HICK. The minimum level of WTP for PORT to be considered cost-effective, compared with PICC, is £10,500 (Scenario 5, Table 15).

Our Value of Implementation analysis suggests that PORT, compared with HICK or PICC, are likely to be considered a cost-effective use of resources based on a range of plausible implementation scenarios. Further details are given in Supplementary Material, Section 3.

Table 15: Value of Implementation results

PORT, compared with HICK		
Scenario	**Question**	**Result**
Scenario 1	What is the value of full implementation?	£24m (95% credibility interval: £22m, £27m).
	What is the value of 50% implementation?	£12m (95% credibility interval: £11m, £13m).
Scenario 2	What level of implementation is required for benefits > costs?	Threshold: any level of implementation > 0. The Value of Implementation at a threshold of 0.01 implementation is £240,000 (95% credibility interval: £222,000, £257,000).
Scenario 3	What is the maximum cost of implementation allowable for benefits > costs?	Threshold: implementation cost of £24m. The Value of Implementation, at implementation cost of £24m, is £179,000 (95% credibility intervals: £-2m, £3m).
Scenario 4	What is the maximum cost of implementation allowable for benefits > costs, if we offer Ports to 50% of patients	Threshold: implementation cost of £12m. The Value of Implementation, at implementation cost of £12m, is £90,000 (95% credibility intervals: £-1m, £2m).
Scenario 5	What is the minimum willingness to pay (WTP) for infections avoided for benefits > costs?	Threshold: £0 WTP. The Value of Implementation, at implementation cost of £2,557, is £5m (95% credibility intervals: £3m, £7m).
PORT, compared with PICC		
Scenario	**Outcome**	**Result**
Scenario 1	What is the value of full implementation?	£800,000 (95% credibility interval: £200,000, £1.2m).
	What is the value of 50% implementation?	£400,000 (95% credibility interval: £130,000, £630,000).
Scenario 2	What level of implementation is required for benefits > costs?	Threshold: any level of implementation > 0. The Value of Implementation at threshold of 0.01 implementation is £2,500 (95% credibility interval: £-3,000, £7,000).
Scenario 3	What is the maximum cost of implementation allowable for benefits > costs?	Threshold: implementation cost of £800,000. The Value of Implementation, at implementation cost of £800,000, is £14,200 (95% credibility intervals: £-500,000, £500,000).
Scenario 4	What is the maximum cost of implementation allowable for benefits > costs, if we offer Ports to 50% of patients	Threshold: implementation cost of £400,000. The Value of Implementation, at implementation cost of £400,000, is £7,000 (95% credibility intervals: £-275,000, £265,000).
Scenario 5	What is the minimum willingness to pay (WTP) for infections avoided for benefits > costs?	Threshold: £10,500 WTP. The Value of Implementation, at implementation cost of £5,602, is £59,363 (95% credibility intervals: £-500,000, £500,000).

5.7 Discussion

Our cost-consequence analysis found that PORT was superior to both HICK and PICC for the majority of our outcomes of interest. While PORT was more costly to insert, when time on device was taken into account, the mean total cost of a PORT was lower than that of a HICK and comparable with PICC. Using the Value of Implementation framework, we have shown that the introduction of a PORT service is likely to be considered cost-effective, compared with either a HICK or PICC service, in routine clinical practice. That is, the benefit of PORT, in terms of the monetary value we place on avoiding infection, is greater than the cost of implementing a PORT service.

Cost-effectiveness, expressed as the incremental cost-per-QALY gained, is one of the most important factors for decision-makers considering implementing a new technology in the UK. A previous analysis of the CAVA trial, based on a cost-per-QALY approach, found that there was significant uncertainty regarding the cost-effectiveness of PORT – driven by a lack of difference in QALY gain between devices (204). This may be because for complex intervention, such as medical devices, the cost-per QALY framework is limited in its ability to capture the broad range of clinical and economic consequences which are of interest to decision-makers and patients. The Medical Research Council (MRC) recently recommended that implementation should be considered alongside economic evaluation when evaluating a complex intervention (30). However, there is currently no clear guidance on how implementation should be incorporated within economic evaluation. In this study, the use of a cost-consequence analysis, alongside a Value of Implementation analysis, allowed us to build on the previous economic evaluation of PORT and to enhance the evidence based by considering a wider range of outcomes which are relevant to both patients and decision-makers.

The original analysis of the CAVA trial found that patients on a PORT were approximately half as likely to experience a complication, compared with a HICK or

PICC (203). Using both direct and indirect evidence, and adjusting our analysis for catheter dwell time, we found that patients were over twice as likely to avoid a complication on a PORT, compared with a HICK, and over three times as likely to avoid a complication compared with a PICC.

The original analysis of the CAVA trial found that the total cost of PORT, including device insertion and follow-up cost, was greater than HICK and PICC (203). However, the CAVA trial found that median dwell time was approximately double on a PORT, compared with HICK and PICC (203). When adjusted for dwell time, PORT was less expensive that HICK or PICC. This study confirmed this finding. This also aligns with the findings of Taxbro et al. (2019) (202) which found that PORT were 34 euros less costly, per day with device in situ, compared with a PICC. Two other studies also found a lower cost associated with PORT, compared with HICK (197, 200). However, in contrast with these three studies, the lower cost of PORT was not due to a reduction in complication cost. The CAVA trial found that PORT was more costly for device insertion, follow-up costs and total costs. It was only when device dwell time was taken into account that PORT was less costly. However, it should be noted that in the CAVA trial, unplanned inpatient and outpatient visits (during follow-up) were taken as a proxy for device-related complication costs. However, it is not clear if these visits were strictly related to the device or not.

The Value of Implementation approach typically uses the expected mean cost difference and QALY gain for a patient as a measure of the "effect" from using the technology and compares this with the cost of setting-up and delivering this technology. However, as we have highlighted, the cost-per-QALY approach is not always suitable for the evaluation of medical devices. For this reason, we included infections avoided, alongside cost, as our measure of effect from the technology. We used £16,095 as our willingness to pay to avoid infections, as this is the financial consequence of hospitalisation and treatment associated with infection. However, it

should be noted, that this monetary cost is not the only consequence of infection. There is an additional quality of life impact on a patient associated with infection. The benefit of avoiding this has not been captured in this WTP estimate. As such, the £16,095 value is likely to be an underestimate of the true value of avoiding an infection.

In common practice, patients requiring a venous access device for planned length of treatment greater than six months are considered for a PORT. Our results suggest that PORT is superior (more effective, less costly) compared with HICK and cost-effective (more effective, similar cost) compared with PICC for patients requiring long-term (≥12 weeks) anti-cancer therapy for solid malignancy. PORT should therefore be considered, alongside PICC, as a safe and cost-effective device option for this patient population.

A future challenge is to configure service delivery such that PORT insertion and removal services become more widely available and able to provide a timely and cost-effective service. This may mean grouping procedures into sessions where adequately trained staff (doctors, surgeons, radiologists, and nurses) can process procedures quickly and safely. With ultrasound, ECG catheter guidance and other advances, such procedures may no longer need to be performed in expensive theatre or angio suite environments. A nurse-led service, in line with what is currently provided at The Christie NHS Foundation Trust, would be one way to achieve a more cost-effective model of care.

The CAVA trial found that, despite having an overall lower number of complications, PORT was associated with a greater number of infections compared with PICC (203). Taxbro et al (2019) found similar findings (201). However, both CAVA and Taxbro reported that when adjusted for device dwell time PORT had a lower infection rate than PICC in both trials. Further research into the cause of PORT-related infection, and

how this can be minimised through improved insertion and removal techniques is warranted. Due to the small number of haematological cancer patients in the CAVA trial, the clinical- and cost-effectiveness of PORT remains unclear for patients requiring long-term anti-cancer therapy in this population.

5.8 Conclusion

In this study we have shown how the use of cost-consequence analysis can overcome the limitations of the cost-utility framework in the evaluation of complex interventions. Our findings suggest that PORT is both safer and, when catheter dwell time is taken into account, comparable in terms of cost. PORT is therefore likely to be cost-effective use of NHS resources. Decision-makers should consider introducing PORT into the suite of venous access device options available for patients in the UK NHS.

5.9 Supplementary material

Section 1: Details of network meta-analysis methods

Structure of the network

There were 1,061 participants in the CAVA trial. Patients were recruited via four randomisation options. The following number of patients were included in each randomisation option: 265 in PORT v PICC v HICK, 212 in PICC v HICK, 397 in PORT v HICK, and 187 in PORT V PICC comparison.

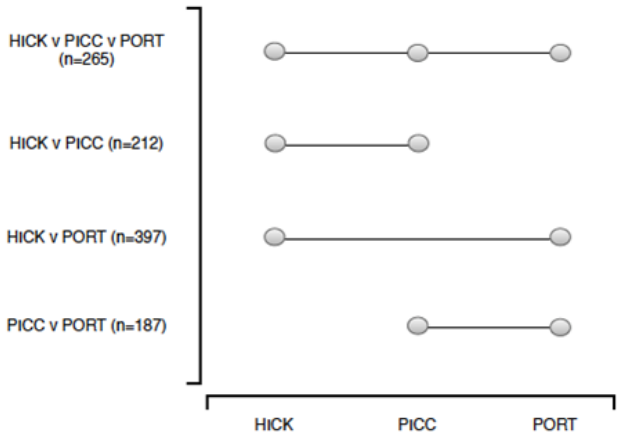


Figure 18: Network of evidence for each VAD in CAVA trial

Each VAD is directly compared with each other, therefore, there is direct and indirect evidence for all three devices. A graphical illustration of the network is given in Figure 18. An assessment of inconsistency via node splitting found that there was no significant difference between direct and indirect evidence for most outcomes. Only for health utilities was there a significant difference between the direct and indirect evidence for the HICK Vs. PICC and PICC Vs. PORT comparisons.

Procedure to combine results from network

We used a two-stage approach to perform the individual participant data network meta-analysis. In the first stage, we used the individual participant data from the four

randomisation options in the CAVA trial to estimate summary measures for each study for each outcome of interest. The aggregate outcome data obtained were combined in the second stage of network meta-analysis. The network meta-analysis was implemented using the 'mvmeta' package in Stata. This is a frequentist approach to multivariate meta-analysis.

Assessment of inconsistency and transitivity

Not all sites within the CAVA trial offered all three VAD options. Each site offered one of the following randomisation option (HICK V PICC V PORT, HICK V PICC, HICK V PORT, and PICC V PORT). An assumption underlying NMA is that effect modifiers are similarly distributed across comparisons in the network. All participants within the CAVA trial had to meet the same inclusion and exclusion criteria to be included within the trial. Therefore, because the data are obtained from a single multi-arm trial, we assume that the effect modifiers are equally distributed across comparisons and that every participant had an equal chance of being randomised to any of the treatment arms in the network. A violation of transitivity may be identified in the network as an inconsistency between direct and indirect evidence. We assumed the networks to be consistent as they were derived from one single multi-arm trial. We evaluated the consistency assumption statistically by comparing the difference between the direct and the indirect treatment effect estimate for loops of evidence by node splitting.

Summary measure results for each comparison from each study

Table 16 present the raw effect estimates obtained from step one of the IPD NMA process. Columns 3-5 represent the first randomisation option, that is, where patients were randomised between HICK, PICC and PORT at a single site. We split this three-way comparison into three two-way comparisons. Columns 6-8 represents the other possible two-way comparisons (PORT V PICC, PICC V HICKMAN, and PORT V HICK) available at other sites. These raw effect estimates are then combined in step two of the IPD NMA.

Table 16: Summary measure results for each comparison from each study

Outcome (expressed as differences)		PICC – Hickman*	Port – Hickman*	Port – PICC*	Port – PICC*	PICC – Hickman*	Port – Hickman*
Randomisation option (3 or 2-way comparison)		3-way comparison			2-way	2-way	2-way
Complication	Difference	0.462	-1.372	-1.984	-0.942	0.317	-0.688
	Standard error	0.239	0.308	0.349	0.324	0.215	0.216
Infection	Difference	-1.427	-1.317	0.075	-0.426	-0.650	-1.127
	Standard error	0.443	0.412	0.551	0.594	0.317	0.284
Non-infection	Difference	1.163	-1.266	-2.618	-1.092	0.848	-0.445
	Standard error	0.282	0.379	0.385	0.365	0.268	0.263
Chemotherapy delay	Difference	-2.691	-1.666	1.346	-1.654	-0.990	-0.767
	Standard error	0.552	0.772	0.871	0.758	0.558	0.641
Unplanned device removal	Difference	0.062	-0.249	-0.324	-0.151	0.137	-0.200
	Standard error	0.068	0.076	0.077	0.083	0.070	0.050
Health utilities	Difference	-0.005	-0.021	-0.011	-0.030	-0.006	0.018
	Standard error	0.011	0.011	0.012	0.011	0.011	0.008
Device insertion cost	Difference	-604.15	325.52	923.99	947.51	-623.26	396.59
	Standard error	29.45	46.51	55.18	36.77	25.05	25.92
Follow-up cost	Difference	-109.69	-203.18	-79.96	-394.36	-161.07	-49.93
	Standard error	98.87	129.69	47.51	482.76	114.49	56.53
Total Cost	Difference	-58.25	-146.35	-70.08	-84.62	-185.70	-50.36
	Standard error	91.42	69.92	78.19	119.31	133.64	55.32

*Reference device

(Note: the first three head-to-head comparisons in the table columns are pairwise comparisons obtained from splitting a 3-way randomised group. In doing so, we incorporated the covariance between the effect estimates in the 3-arm trial to account for correlation.)

Forest plots from the NMA for each outcome of interest

Step two of the IPD NMA, where the raw effect estimates are combined in meta-analysis, is shown in Figures 19-27. Study 1 (vertical axis) refers to randomisation option 1 (3-way randomisation) in Table 16 (columns 3-5), study 2 refers to randomisation option 2 (column 6), study 3 refers to randomisation option 3 (column 7) and study 4 refers to randomisation option 4 (column 8).

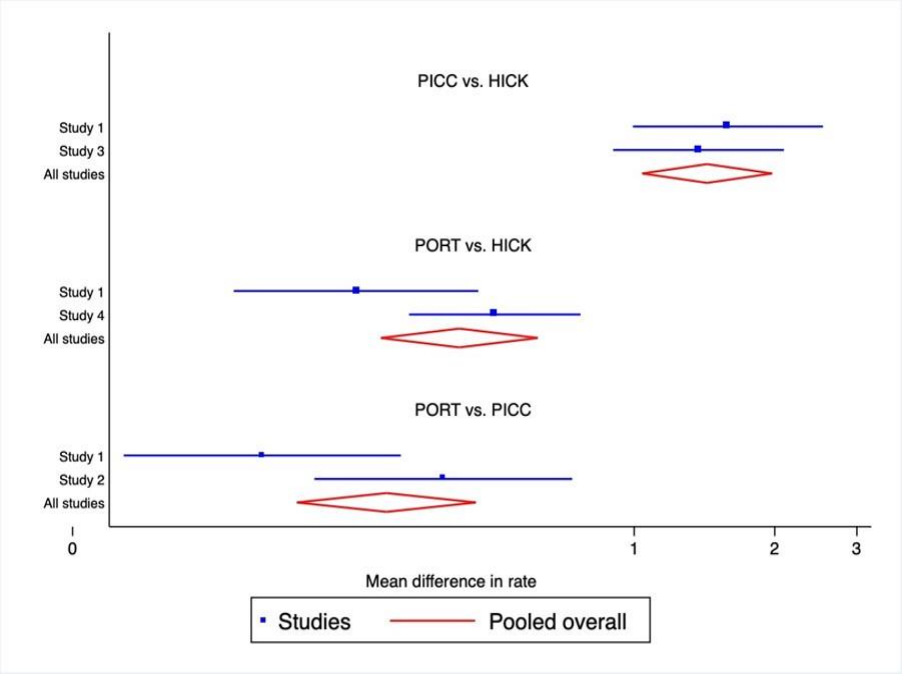


Figure 19: Forest plot for complications

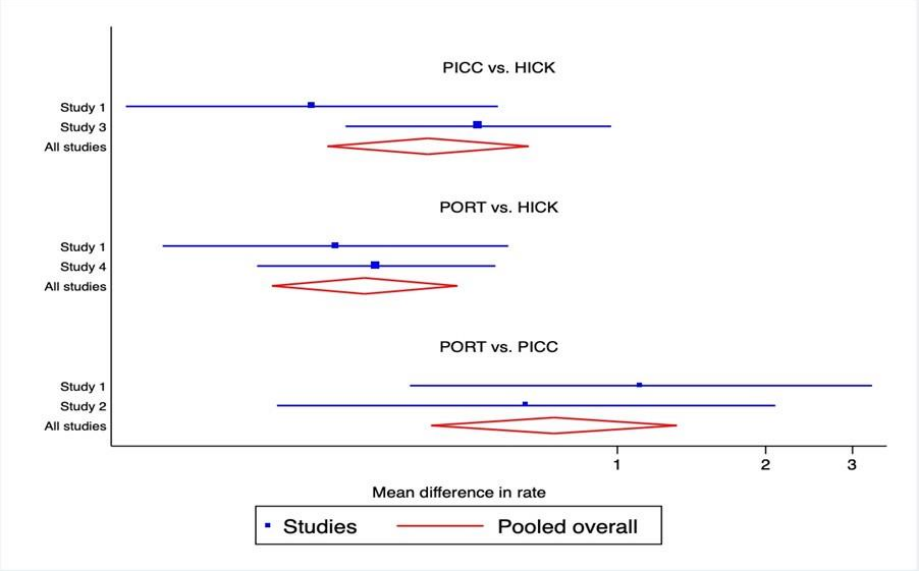


Figure 20: Forest plot for infections

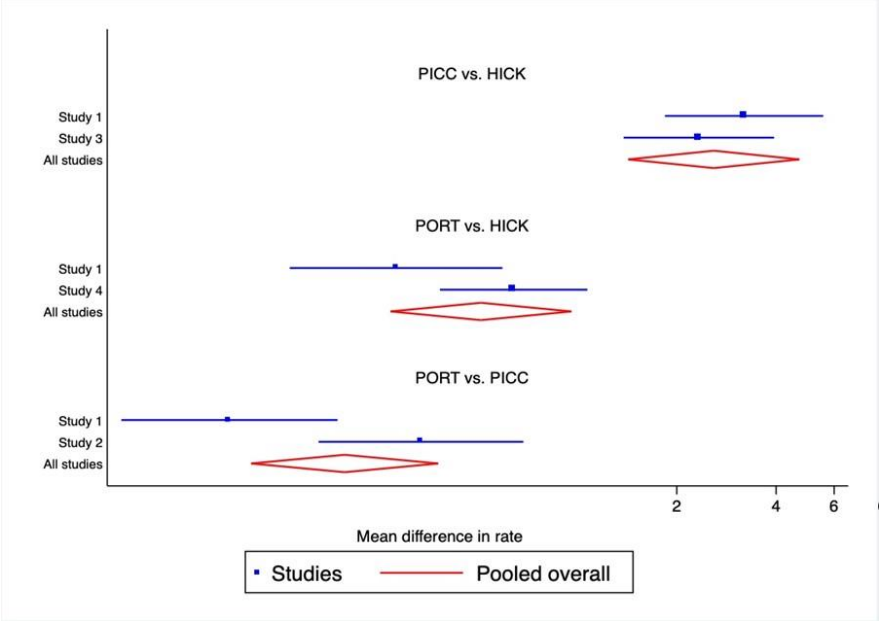


Figure 21: Forest plot for non-infections

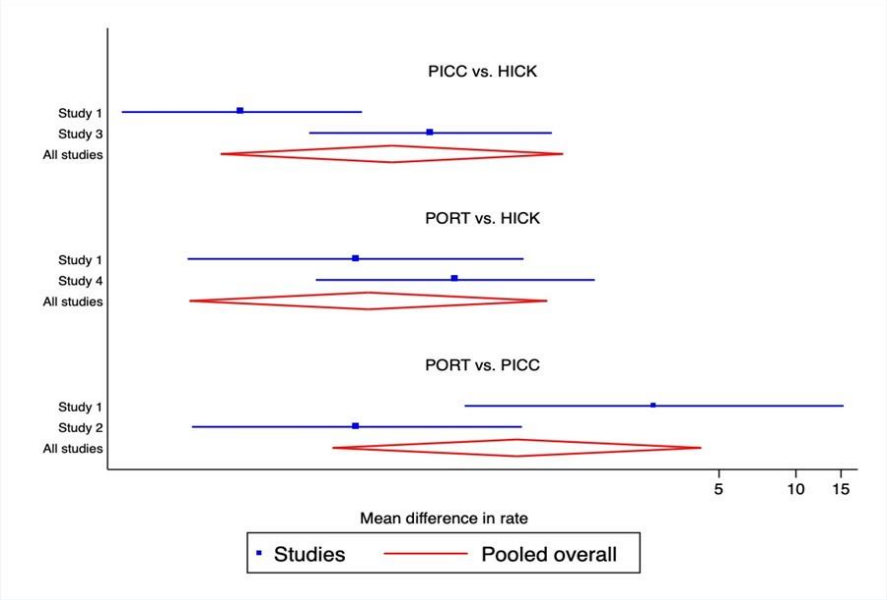


Figure 22: Forest plot for number of days chemotherapy interruption

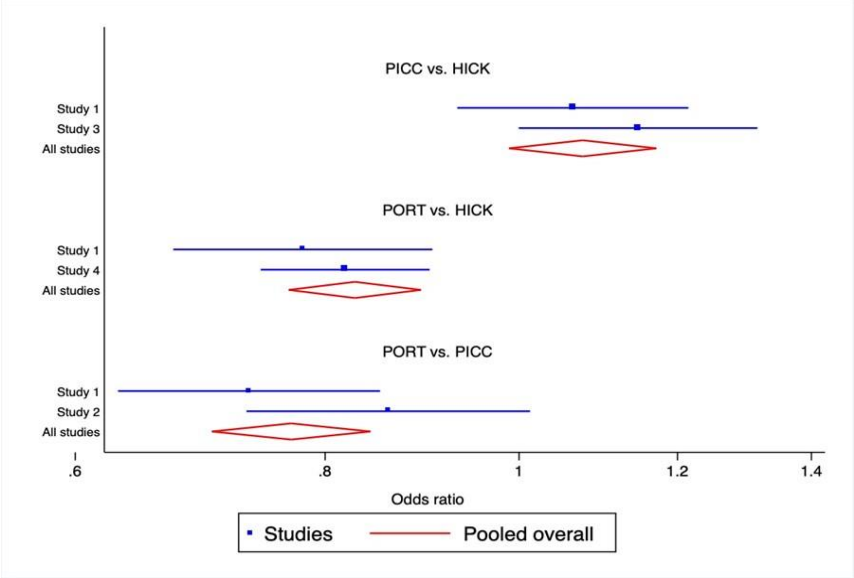


Figure 23: Forest plot for unplanned device removal

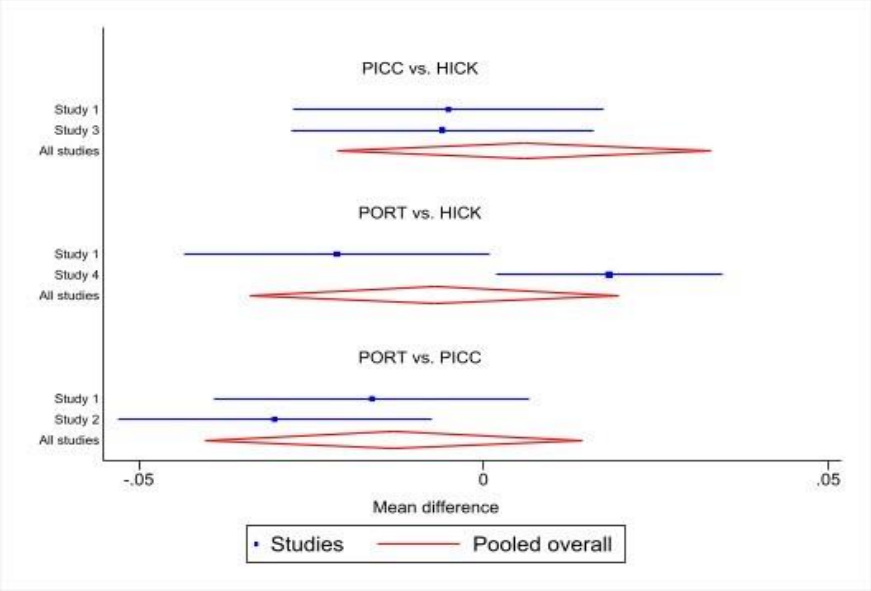


Figure 24: Forest plot for health utilities

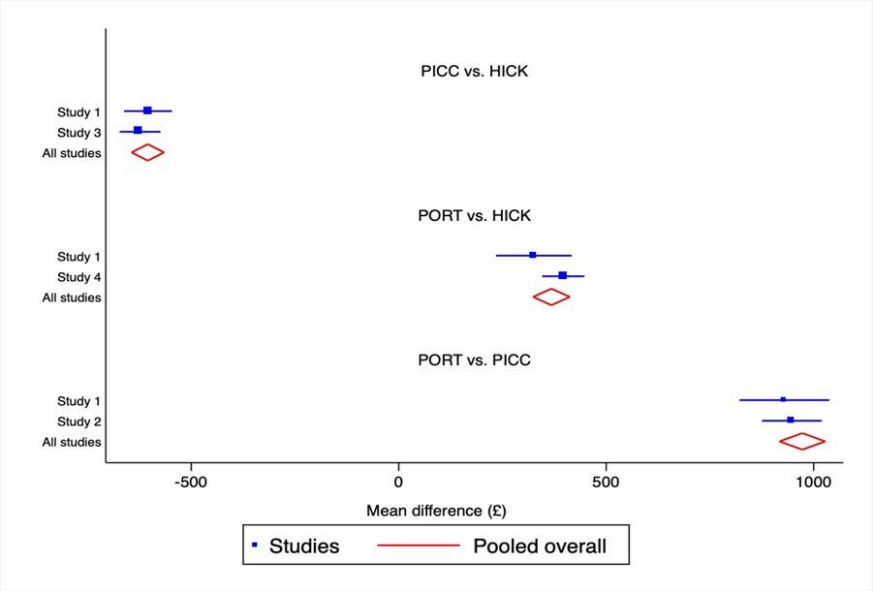


Figure 25: Forest plot for device insertion cost

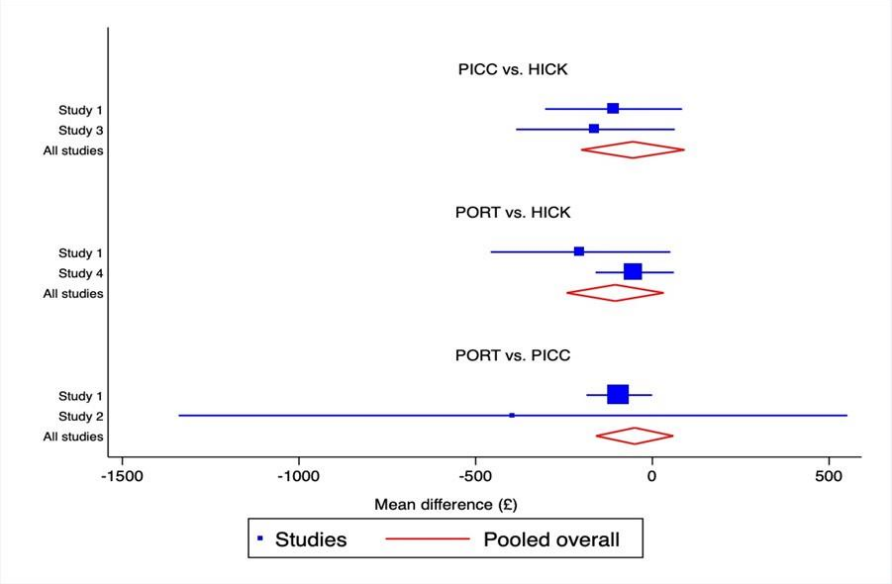


Figure 26: Forest plot for follow-up cost

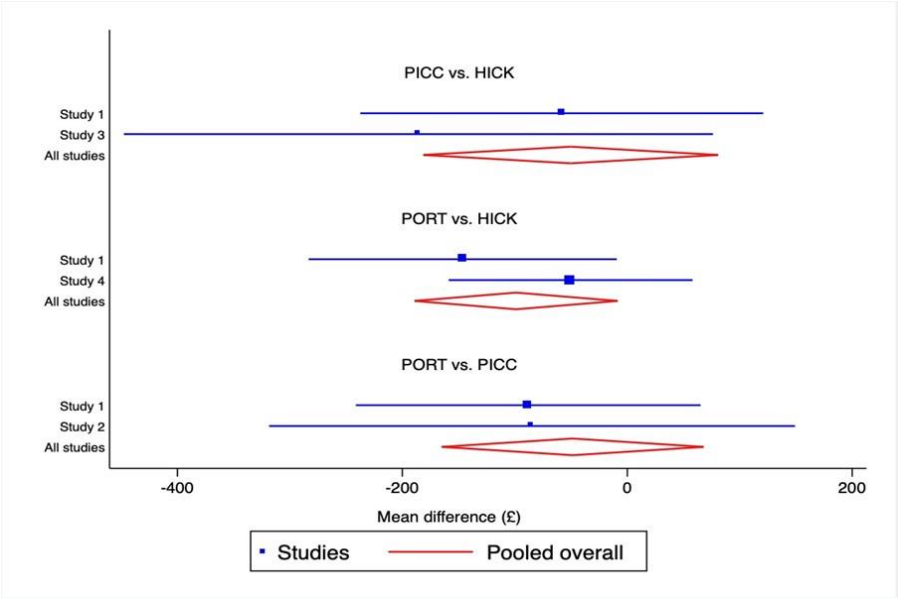
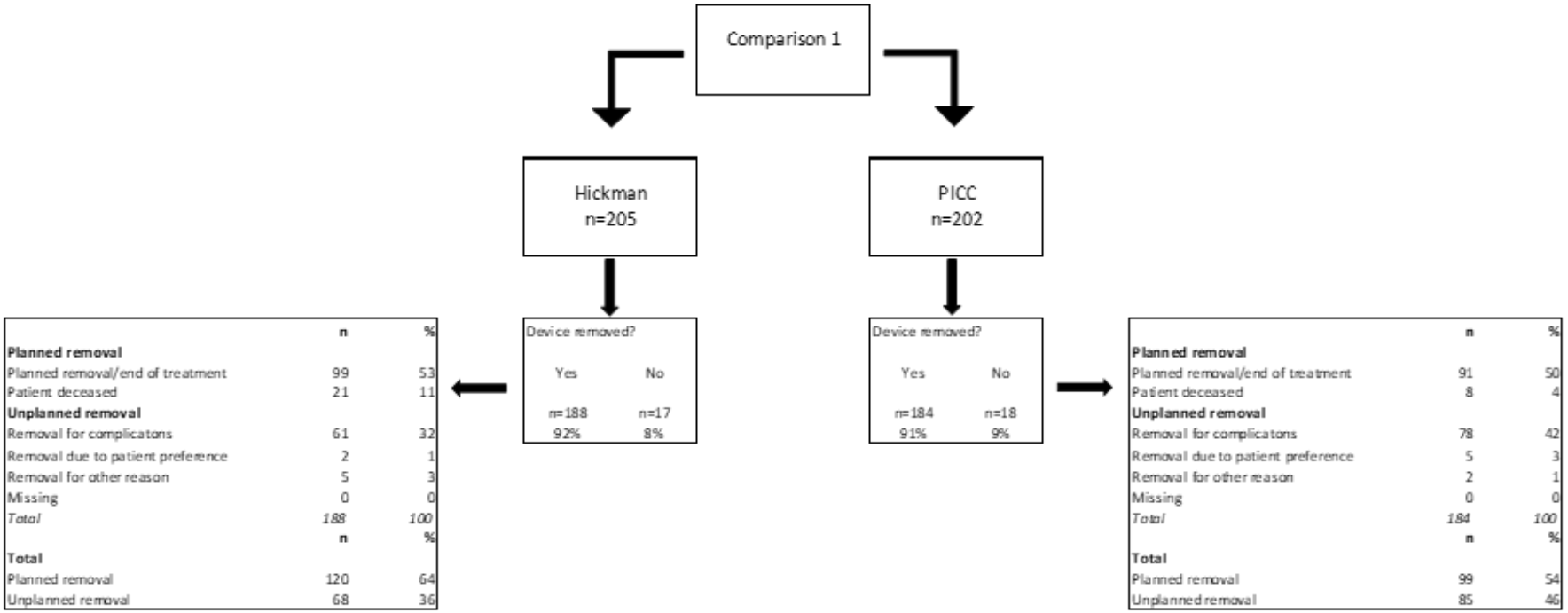


Figure 27: Forest plot for total cost

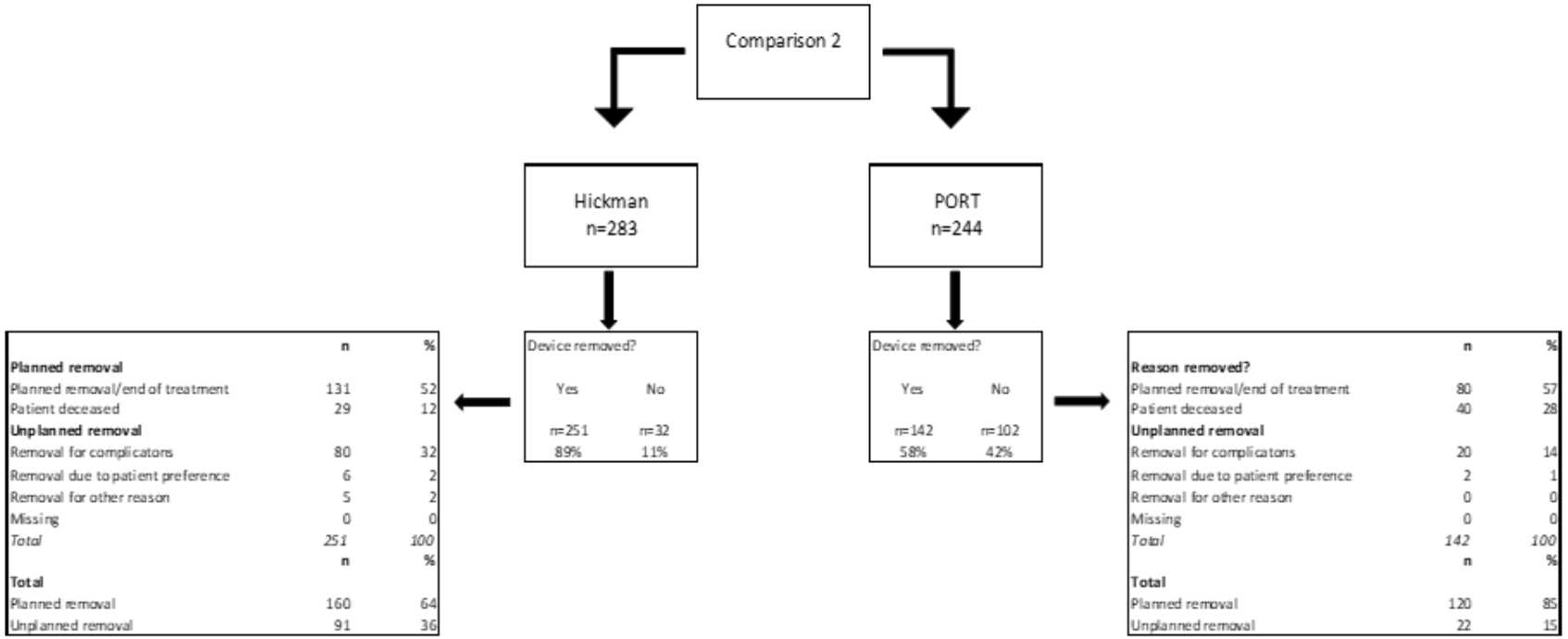
Section 2: Unplanned device removal



	n	%
Planned removal		
Planned removal/end of treatment	99	53
Patient deceased	21	11
Unplanned removal		
Removal for complicatons	61	32
Removal due to patient preference	2	1
Removal for other reason	5	3
Missing	0	0
Total	*188*	*100*
	n	**%**
Total		
Planned removal	120	64
Unplanned removal	68	36

	n	%
Planned removal		
Planned removal/end of treatment	91	50
Patient deceased	8	4
Unplanned removal		
Removal for complicatons	78	42
Removal due to patient preference	5	3
Removal for other reason	2	1
Missing	0	0
Total	*184*	*100*
	n	**%**
Total		
Planned removal	99	54
Unplanned removal	85	46

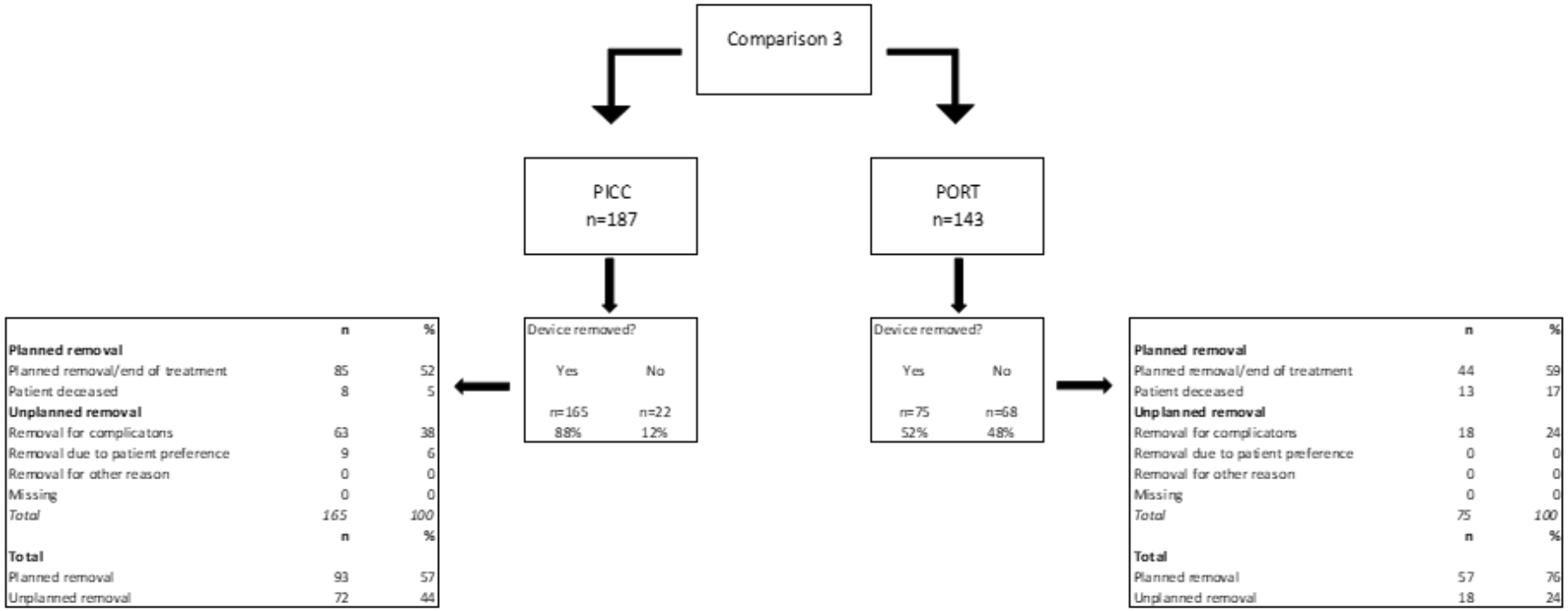
Figure 28: Reasons for device removal in Hickman V PICC comparison from CAVA trial



	n	%
Planned removal		
Planned removal/end of treatment	131	52
Patient deceased	29	12
Unplanned removal		
Removal for complicatons	80	32
Removal due to patient preference	6	2
Removal for other reason	5	2
Missing	0	0
Total	*251*	*100*
	n	**%**
Total		
Planned removal	160	64
Unplanned removal	91	36

	n	%
Reason removed?		
Planned removal/end of treatment	80	57
Patient deceased	40	28
Unplanned removal		
Removal for complicatons	20	14
Removal due to patient preference	2	1
Removal for other reason	0	0
Missing	0	0
Total	*142*	*100*
	n	**%**
Total		
Planned removal	120	85
Unplanned removal	22	15

Figure 29: Reasons for device removal in Hickman V PORT comparison from CAVA trial



	n	%
Planned removal		
Planned removal/end of treatment	85	52
Patient deceased	8	5
Unplanned removal		
Removal for complicatons	63	38
Removal due to patient preference	9	6
Removal for other reason	0	0
Missing	0	0
Total	*165*	*100*
	n	**%**
Total		
Planned removal	93	57
Unplanned removal	72	44

	n	%
Planned removal		
Planned removal/end of treatment	44	59
Patient deceased	13	17
Unplanned removal		
Removal for complicatons	18	24
Removal due to patient preference	0	0
Removal for other reason	0	0
Missing	0	0
Total	*75*	*100*
	n	**%**
Total		
Planned removal	57	76
Unplanned removal	18	24

Figure 30: Complications - % contribution of direct and indirect evidence to combined estimate

Section 3: Value of Implementation analysis

I worked with clinicians at The Beatson Institute for Cancer Research and The Christie NHS Foundation Trust to develop a plausible scenario for the delivery of a PORT via a nurse-led service. The resource items included, and assumptions regarding the procedure time required for staff and setting, where based on expert elicitation. Details of the resource requirements for the delivery of a HICK, PICC and PORT are given in Table 18. Table 19 presents the same analysis as presented in Table 15 in the main text, however, additional details have been included in Table 19.

For all scenarios considered in Table 19, calculations were undertaken using base case values for every parameter (Table 17), while varying only the parameter explicitly under consideration in each scenario, to establish a threshold value. That is, we identify a threshold (or "break-even") value, which is the lowest or highest value at which the Value of Implementation estimate flips from positive to negative (cost-effective to not cost-effective). Once a threshold value was established, we conducted a probabilistic sensitivity analysis to determine how sensitive our results were to the cost and effect parameters included in the model. For example, in Scenario 2 (PORT v HICK comparison), we identify 0.01% level of uptake (e.g. any positive level of uptake), to be associated with a positive Value of Implementation estimate. We then undertake PSA around this estimate, varying parameters for the difference in treatment cost and difference in infection rate. For Scenario 3, we varying the level of initial implementation (e.g. set up) cost. We find that the maximum cost of implementation, for which the Value of Implementation will be positive, is £24m (PORT v HICK comparison).

Table 17: Base case parameter values for Value of Implementation analysis

Inputs	Hickman	PICC
Number of patients eligible for VAD at single oncology centre over 5 years	5,000	5,000

Effective (discounted) population	4,673	4,673
Utilisation following implementation activity	100%	100%
Willingness to pay for infections avoided	£16,095	£16,095
Difference in number of infections avoided	0.242	0.03
Difference in procedure cost	£-937	£268
Difference in cost of implementation over 5 years	£2,557	£5,602

Parameter values above were used in the following Value of Implementation equation:

$N(\sigma-\rho) * ((WTP*\Delta \text{ Infections}) - \Delta C1) - C2 > 0$

Where:

N = patient population, σ = utilisation following implementation activity, ρ = current level of utilisation, WTP = willingness to pay for infections avoided, Q = number of infections avoided, C1 = cost per procedure, C2 = implementation cost.

Table 18: Proposed scenarios for implementation of Hickman, PICC and Port service in routine practice

HICK PICC and PORT fixed and variable costs

HICKMAN

Resource	Quantity	Unit cost	% required	Cost
Procedure time (30 mins)			0.50	
Device Cost	1	£165	1.00	£165
staff				
nurse	2	£58		£116
radiographer	0	£82		£0
anesthesiologist	0	£119		£0
radiologist	0	£109		£0
setting				
theatre	0	£571		£0
procedure/treatment room	1	£0		£0
radiology dept	0	£571		£0
bedside	0	£0		£0
anesthesia used				
local only	1	£11		£11
local and conscious sedation	0	£11		£0
general anesthesia	0	£35		£0
imaging				
fluoroscopy	0	£168		£0
x-ray	0	£33		£0
ultrasound	0	£60		£0
sherlock tracking system	0	£11		£0
ECG	1	£199		£100
type of dressing				
non-anti-microbial	1	£0		£0
anti-microbial	0	£0		£0
Device removal cost				
HICK (nurse, procedure toom, 25 mins, 100% of patients)	1	£58	0.42	£24
Device replacement cost:				
insertion + device cost			0.80	£333
Complications (follow-up) costs				£1,911
Total insertion cost				**£748**
Total insertion cost + complication costs				**£2,659**
Flushing cost:				
Hick (23 weeks dwell time) (weekly flush, nurse, 3 home visits (1 hour) + 1 at oncology site per month (15 mins))	23	£58	0.75	£1,001
	23	£58	0.25	£1,334
				£2,335
Implementation costs over 1 year:				***£2,335***
Cost over subsequent 4 years:				***£9,338***
Implementation costs over 5 year:				***£11,673***

PICC

Resource	Quantity	Unit cost	% required	Cost
Procedure time (30 mins)			0.50	
Device Cost	1	£120	1.00	£120
staff				
nurse	1	£58		£58
radiographer	0	£82		£0
anesthesiologist	0	£119		£0
radiologist	0	£109		£0
setting				
theatre	0	£571		£0
procedure/treatment room	1	£0		£0
radiology dept	0	£571		£0
bedside	0	£0		£0
anesthesia used				
local only	1	£11		£11
local and conscious sedation	0	£11		£0
general anesthesia	0	£35		£0
imaging				
fluoroscopy	0	£168		£0
x-ray	0	£33		£0
ultrasound	0	£60		£0
sherlock tracking system	0	£11		£0
ECG	1	£199		£100
type of dressing				
non-anti-microbial	1	£0		£0
anti-microbial	0	£0		£0
Device removal cost				
PICC (nurse, procedure room, 10 mins, 100% of patients)	1	£58	0.17	£10
Device replacement cost:				
insertion + device cost			0.90	£268
Complications (follow-up) costs				£887
Total insertion cost				**£567**
Total insertion cost + complication costs				**£1,454**
Flushing cost:				
PICC (17 weeks dwell time) (weekly flush, nurse, 3 home visits (1 hour) + 1 at oncology site per month (15 mins))	17	£58	0.75	£740
	17	£58	0.25	£986
				£1,726
Implementation costs over 1 year:				***£1,726***
Cost over subsequent 4 years:				***£6,902***
Implementation costs over 5 year:				***£8,628***

PORT

Resource	Quantity	Unit cost	% required	Cost
Procedure time (50 mins)			0.83	
Device Cost	1	£340	1.00	£165
staff				
nurse	2	£58		£116
radiographer	0	£82		£0
anesthesiologist	0	£119		£0
radiologist	0	£109		£0
setting				
theatre	0	£571		£0
procedure/treatment room	1	£0		£0
radiology dept	0	£571		£0
bedside	0	£0		£0
anesthesia used				
local only	1	£11		£11
local and conscious sedation	0	£11		£0
general anesthesia	0	£35		£0
imaging				
fluoroscopy	0	£168		£0
x-ray	0	£33		£0
ultrasound	0	£60		£0
sherlock tracking system	0	£11		£0
ECG	1	£199		£166
type of dressing				
non-anti-microbial	1	£0		£0
anti-microbial	0	£0		£0
Device removal cost				
PORT (nurse, procedure toom, 25 mins, 70% of patients)	1	£58	0.29	£17
Device replacement cost:				
insertion + device cost				£0
Complications (follow-up) costs				£1,247
Total insertion cost				**£475**
Total insertion cost + complication costs				**£1,722**
Flushing cost:				
Port (54 weeks dwell time) (monthly flush, nurse, 3 home visits (1 hour) + 1 at oncology site per month (15 mins))	12	£58	0.75	£522
	12	£58	0.25	£696
				£1,218
Device insertion training costs				
Supervised procedures:	25			
No. of nurses (training):	5			
Cost of nurse time to train:		£58		
Procedure time (50 mins):			0.83	
				£6,042
Device access training costs				
Phantom - Chester Chest	1	£1,362		£1,362
Huber needle (1 per trainee)	5	£5		£23
Additional sundries	1	£5		£5
Clinical educator	1	£61	4	£244
				£1,634
A&E cover training costs				
(two grade 7 nurses receiving training on accessing Ports, half day (4 hrs) required)				
No of nurses:	2			
Cost of nurse time to train:		£58	4	
				£464
Implementation costs over 1 year:				***£9,357***
Cost over subsequent 4 years:				***£4,872***
Implementation costs over 5 year:				***£14,229***

**training costs apply in year 1 only*

Incremental costs of Port, compared with Hick	
difference in procedure cost per patient:	-£937
difference in implementation costs over 5 years	£2,557

Incremental costs of Port, compared with PICC	
difference in procedure cost per patient:	£268
difference in implementation costs over 5 years	£5,602

Table 19: Value of Implementation analysis - the value of implementing Hickman or PICC, compared with Ports

Port, compared with Hickman				
Scenario #	**Type of sensitivity analysis**	**Outcome**	**Parameters varied**	**Result**
Scenario 1	PSA	Value of full implementation Value of 50% implementation	Costs and number of infections avoided	£24m (95% credibility interval: £22m, £27m) £12m (95% credibility interval: £11m, £13m).
Scenario 2	Threshold analysis and PSA	Level of implementation required for benefits > costs	Threshold: level of implementation, PSA: costs and number of infections avoided (at given threshold)	Threshold: any level of implementation > 0. The value of Implementation at a threshold of 0.01 implementation is £240,000 (95% credibility interval: £222,000, £257,000).
Scenario 3	Threshold analysis and PSA	Maximum cost of implementation possible for benefits > costs	Threshold: implementation cost, PSA: costs and number of infections avoided (at given threshold)	Threshold: implementation cost of £24m. The Value of Implementation, at implementation cost of £24m, is £179,000 (95% credibility intervals: £-2m, £3m).
Scenario 4	Threshold analysis and PSA	Maximum cost of implementation possible for benefits > costs, if we offer Ports to 50% of patients	Threshold: implementation cost, PSA: costs and number of infections avoided (at given threshold)	Threshold: implementation cost of £12m. The Value of Implementation, at implementation cost of £12m, is £90,000 (95% credibility intervals: £-1m, £2m).

Scenario 5	Threshold analysis and PSA	Minimum willingness to pay (WTP) for infections avoided for benefits > costs	Threshold: WTP PSA: Costs and number of infections avoided (at given threshold)	Threshold: £0 WTP. The Value of Implementation, at implementation cost of £2,557, is £5m (95% credibility intervals: £3m, £7m).
Port, compared with PICC				
Scenario #	**Type of sensitivity analysis**	**Outcome**	**Parameters varied**	**Result**
Scenario 1	PSA	Value of full implementation Value of 50% implementation	Costs and number of infections avoided	£800,000 (95% credibility interval: £200,000, £1.2m) £400,000 (95% credibility interval: £130,000, £630,000).
Scenario 2	Threshold analysis and PSA	Level of implementation required for benefits > costs	Threshold: level of implementation, PSA: costs and number of infections avoided (at given threshold)	Threshold: any level of implementation > 0. The Value of Implementation at threshold of 0.01 implementation is £2,500 (95% credibility interval: £-3,000, £7,000).
Scenario 3	Threshold analysis and PSA	Maximum cost of implementation possible for benefits > costs	Threshold: implementation cost, PSA: costs and number of infections avoided (at given threshold)	Threshold: implementation cost of £800,000. The Value of Implementation, at implementation cost of £800,000, is £14,200 (95% credibility intervals: £-500,000, £500,000).
Scenario 4	Threshold analysis and PSA	Maximum cost of implementation possible for benefits > costs, if we	Threshold: implementation cost,	Threshold: implementation cost of £400,000. The Value of Implementation, at implementation cost of £400,000, is £7,000 (95% credibility intervals: £-275,000, £265,000).

		offer Ports to 50% of patients	PSA: costs and number of infections avoided (at given threshold)	
Scenario 5	Threshold analysis and PSA	Minimum willingness to pay (WTP) for infections avoided for benefits > costs	Threshold: WTP PSA: Costs and number of infections avoided (at given threshold)	Threshold: £10,500 WTP. The Value of Implementation, at implementation cost of £5,602, is £59,363 (95% credibility intervals: £-500,000, £500,000).

Chapter 6: Discussion and conclusion

6.1 Introduction

This PhD thesis has presented a linked body of work which demonstrates that, while currently underutilised, a range of methods are available for incorporating implementation considerations within the economic evaluation of health technologies. In addition, I have shown, via two real-world case studies, how the inclusion of implementation can allow us to provide research evidence which is more relevant and useful to decision-makers.

A key strength of this PhD thesis is that the topic considered, implementation within the economic evaluation of health technologies, was born out of necessity, rather than academic interest alone. I did not start out on this journey to undertake a PhD, but simply to answer a question – could I provide research evidence which was more useful to decision-makers? In this sense, I hope that the work contained in this PhD can provide a useful first step to other researchers who find themselves asking the same question.

I was fortunate to be involved in two excellent clinical trials – the PISTE trial and the CAVA trial. These trials provided the inspiration for the work contained in this thesis. It is a strength of this thesis that the implementation barriers and scenarios considered in my case studies were directly informed by stakeholders, clinicians and decision-makers working in these areas. Close collaboration within these trials ensured that the questions asked in my case studies were the questions relevant for decision making.

The methods utilised in this PhD are not novel. What was novel was how these methods were used to inform implementation. Implementation is particularly relevant in the context of complex interventions. However, when evaluating complex interventions, the cost-per-QALY framework may be limited in its ability to capture the range of costs and outcomes relevant to patients and decision-makers. In my first case study, I showed how budget impact analysis alongside the Value of Implementation framework could be used to assess the likely

cost-effectiveness of mechanical thrombectomy in routine practice. I also demonstrated that it was not necessary to achieve full implementation to realise the benefits of mechanical thrombectomy. In my second case study I showed how cost-consequence analysis could be used to disaggregate costs and outcomes and allow patients and decision-makers to explicitly trade off the importance they place on these attributes when choosing a venous access device. The Value of Implementation framework was design to estimate the population level total value of implementation, incorporating costs not captured within a traditional analysis. I showed how the Value of Implementation framework could be used to answer additional questions relevant to decision-makers – such as what is the value of delivering PORT to just 50% of patients requiring a VAD? What is the minimum willingness to pay for infections avoided for the benefits of PORT to exceed the cost of implementation?

In this final chapter I discuss specific findings from my literature reviews and case studies, reflect on the implementation of my two case studies in the UK to date, provide suggestions for further research, and suggest the implications of my research for healthcare policy.

6.2.1 Chapter 2 findings, strengths, and weaknesses

Objective 1: Undertake a rapid systematic review of how implementation been incorporated within the NIHR HTA programme in the UK.

I undertook a systematic rapid review of health technologies assessments funded by the NIHR's HTA programme over the preceding six years. An economic evaluation is a core component of a health technology assessment. However, I found that the consideration of implementation alongside economic evaluation was inconsistent. For example, some studies adopted a mixed methods approach, using qualitative research to incorporate additional context to their evaluation. While some studies either did not consider implementation at all, or where it was considered, was considered only as a discussion point or an area for further research. Given that both the National Institute for Health and Care Research and the Medical Research Council both recommend that implementation, to some extent, should be

considered within a health technology assessment, this was a surprising result. One reason for this result may be the lack of well-developed guidance from researchers, reimbursement agencies or funders on exactly how implementation should be incorporated within economic evaluation. Such guidance would need to make clear how this sort of research would be used. For example, who would be the target audience of implementation research? Should implementation be the remit of national reimbursement agencies (such as NICE or the SMC)? Or should this be considered at a local health board level? While it remains unclear how this type of research should be undertaken, or how it would be used by decision-makers, it should not be a surprise that this type of research is not routinely undertaken by researchers.

The main strength of this review relates to the role played by NIHR HTA programme in the UK. Not only is this the biggest funder of health-related research in the UK, but the programme is also specifically targeted towards applied heath research – i.e., research which aims to make a real change to clinical practice. However, the NIHR HTA programme is only one funder of health research in the UK. It is possible that a more extensive search of other databases may have identified methods not included within my review. However, for pragmatic purposes, and due to the prominent role played by the NIHR HTA programme in setting the research agenda in the United Kingdom, I chose to limit my search to this database only.

Another strength of this review is that I was not prescriptive regarding how implementation was considered within the study – all studies which included the term implementation within the title or abstract were included for review. This is also a limitation of my review, as other terms - such as capacity, uptake, utilisation, etc., - are also used in this context. However, since I was primarily focused on how any method used related specifically to the issue of implementation, I believe this was a reasonable approach. However, I acknowledge that broadening the inclusion criteria may have yielded some additional results.

To the best of my knowledge, there is no dedicated checklist or tool for assessing how implementation has been considered within a health technology assessment. In my review I used the Proctor et al. (2012) checklist to organise my findings and to evaluate how implementation had been considered in the studies identified (52). I noted that the Proctor checklist was developed to help researchers with the design of implementation studies, rather than as an assessment of how implementation has been incorporated. However, I felt it was worth using the Proctor checklist to determine to what extent the studies identified would have been deemed sufficient to undertake an implementation study based on Proctor's criteria. However, in recognition of the limitations of the Proctor checklist, a narrative synthesis was used to identified additional themes relevant to the issue of implementation, but not captured within the Proctor checklist.

My review found that relatively basic implementation tools (e.g., stakeholder engagement, process evaluation) were being used in health technology assessments in the UK (100). A range of more sophisticated tools are available from implementation science which could be adapted for use in economic evaluation – for example the frameworks of Glasgow et al. (2019) (24) and Damschroder (2009) (25). Likewise, there are a range of tools from economic evaluation which could contribute towards implementation science – for example the frameworks of Mason (2001) (2) and Fenwick (2008) (5). However, there are a lack of bespoke tools for considering economic evaluation alongside implementation as it relates to health technology assessment. The incorporation of implementation science alongside economic evaluation within a single framework may allow us to begin to bring these two disciplines together. However, guidance and examples of how this can be achieved are still lacking.

6.2.2 Chapter 3 findings, strengths, and weaknesses

Objective 2: Undertake a systematic review to map out which methods are currently available for incorporating implementation considerations within the economic evaluation of health technologies.

In chapter 2 I found that there was limited application of methods for incorporating implementation within the economic evaluation of health technologies funded by the HTA programme in the UK. In chapter 3 I undertook a systematic review to map out any methods which are currently available for incorporating implementation within economic evaluation, how these methods differ, and when these methods might be applied. I found that there were a range of methods currently available, and that these methods could broadly be categorized as focusing on i) policy cost-effectiveness approach, ii) Value of Information (VoI) and Value of Implementation approach, iii) study design approach, iv) and costing of systems change approach. The choice of when to use a particular approach will depend on the decision problem. When the focus is on conducting further research, the methods identified in category ii) and iii) above are most relevant. When the focus is on the value of increasing uptake or service reconfiguration, the methods identified in category i), ii) and iv) are most relevant. Finally, when the focus is on the trade-off between further research and further uptake, methods identified in category ii) are most relevant.

To interpret and understand the position, and role, of the methodologies identified in my review, I categorised my results in terms of four themes or "approaches" to implementation. While I believe that these four approaches do capture the overall purpose of the methodologies identified, it was clear that there was significant overlap among approaches and that many studies categorised as belonging to one group could quite easily be considered part of another group also. Furthermore, one or more of the methods contained within each category may be considered simultaneously. However, I felt such simplifications were necessary to bring order and focus to a literature which is at present disparate and not well sign-posted for researchers.

The conceptual model presented in Chapter 3 maps out the methods identified in my review within the context of the development, evaluation and implementation of a health technology. Our review was limited to methods which specifically combined implementation alongside economic evaluation. However, there are other methods available in the field of

implementation science - such as stakeholder engagement, process evaluation and hybrid efficacy-implementation trials - which are relevant to this process which I have included in the model for completeness. These methods provide a means to capture data related to implementation which may be relevant within an economic evaluation. To incorporate implementation within the economic evaluation of health technologies, it will be important to consider how relevant methods from either discipline can inform a health technology assessment. It is my hope that I, or other researchers in the field, will develop this model further.

The systematic review adopted the "pearl-growing" approach within the search strategy. The process of pearl-growing involves specifying an initial "pearl", reviewing the references and citations of this study, and then reviewing the references and citations of *those* studies, and so on, until the studies returned in your search are no longer relevant. It is possible that an alternative choice of initial pearl would have led to a different final set of studies obtained. However, given that for a relevant study not to be captured within the review, it would need to not have been referenced or cited in any of the most referenced and cited studies in that area, it is unlikely that this process would fail to identify many relevant studies. A degree of subjectivity is involved in the decision to complete the search process at the point at which the studies identified are deemed no longer relevant. However, subjective decisions such as these are not uncommon in systematic review, and any other form of research, and as such I believe are not a significant weakness of this approach.

6.2.3 Chapter 4 findings, strengths, and weaknesses

Objective 3.1: Demonstrate how the Value of Implementation framework can be utilised to provide more useful evidence for decision-makers using two case studies - In the context of mechanical thrombectomy for acute stroke in the UK.

The PISTE clinical trial compared the use of mechanical thrombectomy plus standard care, compared with standard care alone (43). Following the randomization of 65 patients, the trial

was terminated prematurely, due to a lack of clinical equipoise. However, the improvement in clinical outcomes associated with mechanical thrombectomy aligned with that observed in similar trials around this time (155). I was subsequently invited to undertake an economic evaluation of the cost-effectiveness of mechanical thrombectomy plus standard care, compared with standard care only, using data from the PISTE trial. My analysis, along with other similar analyses around the same time, showed mechanical thrombectomy to be highly cost-effective over a lifetime horizon.

Further discussions with the principal investigator on the PISTE trial highlighted a range of issues which were likely to create barriers for the implementation of mechanical thrombectomy into routine clinical practice. These include, but were not limited to, i) the need to reconfigure the clinical pathway for acute stroke such that patients are able to receive mechanical thrombectomy treatment within six hours of stroke onset, ii) the number and location of comprehensive stroke centres and workforce configuration required to treat the eligible population within the required time frame, and iii) the cost of the capital investment required to purchase the biplane angio suite necessary for mechanical thrombectomy.

Given the challenges and uncertainties associated with implementation, I did not feel we were in a position to say whether or not mechanical thrombectomy was likely to be cost-effective when delivered in routine practice, despite the positive results of previous economic evaluations. To help answer this question, I undertook a Value of Implementation analysis for the introduction of mechanical thrombectomy. I began by estimating the cost of setting up a mechanical thrombectomy service at a single comprehensive stroke centre. I incorporated the set-up costs required for the biplane angio suite and training required to perform the procedure. I also included the cost of all staff required to deliver mechanical thrombectomy, alongside assumptions regarding the growth of staffing requirements as patient numbers increased. These costs were scaled-up to the 27 comprehensive strokes centres required to treat the eligible population of the UK. These costs were combined with

the expected QALY benefit of mechanical thrombectomy to estimate the Value of full Implementation and a break-even level of implementation – that is, the level above which the benefit of implementing mechanical thrombectomy into routine practice, in NMB terms, is expected to be greater than the cost. Addressing these additional challenges allowed us to provide more detailed and context-specific evidence for decision-makers considering introducing mechanical thrombectomy. Specifically, this additional evidence meant that decision-makers were better able to plan for the resource requirements necessary to implement this technology in their own setting. It also demonstrated that it was not necessary to achieve full implementation to realise the benefits of mechanical thrombectomy.

The work in this chapter was motivated by a recognition that much was missing from the current evidence base regarding the cost-effectiveness of mechanical thrombectomy in routine practice and a desire to provide evidence which was more useful to decision-makers. While I believe that my study contributed towards this goal, there remains areas of significant uncertainty - either due to a lack of data, or due to a lack of methods to incorporate these issues into an economic evaluation. For example, one of the most significant sources of decision uncertainty in my lifetime model was on the rate at which patients' health status deteriorated post the 90-day trial period. Further follow-up studies in this patient population would reduce this uncertainty. However, political motivations and clinicians' willingness to adopt change continue to present barriers to the implementation of mechanical thrombectomy. Capturing and incorporating these data into an economic evaluation would be challenging.

A limitation of this analysis, and with many analyses, was the lack of consideration of implementation from the outset. There are two main reasons for this. Firstly, quite simply, it was a learning process for me. The issues and challenges associated with implementation had not presented themselves so clearly to me as they did throughout the development of this project. Secondly, the consideration of implementation was not mandated by the

research funder. Therefore, there was no impetus to discuss the issue of implementation at the study outset. The frustrating thing, however, is that the majority of the implementation challenges which faced thrombectomy were known at the outset among clinicians working in acute stroke care. However, a lack of early engagement among all stakeholders involved in evaluating thrombectomy, alongside the lack of guidance from funders and reimbursement agencies, meant that this knowledge was not used to inform the evaluation and implementation of thrombectomy.

The work I did on this project helped to address the challenges identified by the principal investigator on the PISTE trial (outlined at the beginning of this section - 6.2.3). In addition to the work I did, other modelling studies also contributed to our understanding of how mechanical thrombectomy could be implemented. McMeekin et al. (190, 210) estimated the number of patients expected to be eligible for mechanical thrombectomy each year in the UK. Allen et al. (2018) undertook a modelling exercise to determine the optimal organization of stroke services throughout England, given time to treatment requirements, to maximize access to intravenous thrombolysis and mechanical thrombectomy services (176). All of these methods provided some insight into the challenge of how best to implement a cost-effective mechanical thrombectomy service in the UK. Future studies involving complex interventions should consider from the outset the potential challenges the intervention may face regarding implementation in routine practice and what role, if any, stakeholders can play in informing data capture and analysis required to model these challenges. Having this additional evidence - on the initial set up costs, workforce configuration and the changes required to the clinical pathway – would better allow decision-makers to plan for the implementation of thrombectomy in routine practice. Such a proactive, rather than retrospective, approach to implementation may allow for a speedier transition from clinical trials to clinical practice.

6.2.4 Chapter 5 findings, strengths, and weaknesses

Objective 3.2: Demonstrate how the Value of Implementation framework can be utilised to provide more useful evidence for decision-makers using two case studies - In the context of venous access devices for the delivery of anti-cancer therapy in the UK.

The CAVA clinical trial demonstrated the superior safety of PORT, compared with HICK and PICC devices, for the delivery of long-term anti-cancer therapy. A cost-utility analysis alongside the CAVA trial compared the costs and quality-adjusted life-years (QALYs) associated with the use of each device (204). PORT was associated with a small difference in cost (-£45) and QALYs (0.004) compared with Hickman and a large difference in cost (£1,665), but small difference in QALYs (-0.018) compared with PICC. However, a device-specific quality of life measure used within the CAVA study, alongside previous research, suggested a preference for PORT (197-199). Given the complex nature of implementing medical devices, where multiple outcomes may be relevant to multiple stakeholders, the cost-per-QALY metric may not have been suitable for decision making. Furthermore, service provision and delivery varied among sites including within the CAVA trial – that is, not all sites offered all devices, and how these devices were delivered varied among sites also. This heterogeneity in service delivery led to heterogeneity in the cost associated with each device in the study.

For these reasons, the economic evaluation undertaken in this chapter was comprised of two main components. Firstly, I estimated a range of clinical and economic outcomes relevant to patients and decision-makers. Outcomes were estimated using an individual participant data network meta-analysis and presented as a cost-consequence analysis. This enabled me to present my results in a way which allowed patients and decision-makers to determine the importance they place on these attributes when choosing an appropriate device. Such granularity may be more suitable for decision making in the context of a complex intervention and can be lost when decision making is based on a cost-per-QALY framework.

Secondly, I undertook a Value of Implementation analysis to incorporate additional considerations, such as changes to the service delivery for a PORT and the cost of additional training and staff requirements. To inform this, I worked alongside radiologists and nurses within oncology centres at The Beatson (Glasgow) and The Christie (Manchester) to develop a plausible scenario for the delivery of a PORT service.

The insertion of a PICC device is typically "nurse-led" and can be undertaken by the bedside. Whereas HICK and PORT insertion is typically "radiologist-led" and is performed in a theatre setting. However, this pattern of service provision is not homogenous throughout the UK. Rather, a team of clinicians, including radiologists, surgeons, anaesthetists and nurses, provide varying degrees of support, depending on their own centre's care pathway, culture and each clinician's own level of experience with each device. This heterogeneity of service provision and delivery is inherent in the cost of device insertion captured within the CAVA trial. Therefore, "true" cost of inserting a HICK, PICC or PORT in the UK, based on the results of the CAVA trial, are uncertain.

The Christie NHS Foundation Trust in Manchester is the largest single site cancer centre in Europe. In contrast to most other sites in the UK, The Christie offers a fully nurse-led service for the delivery of PORT. This model serves as a template for how PORT can be implemented into routine practice in the NHS in the most cost-effective manner. For this reason, to estimate the Value of Implementation of a PORT service, I undertook my analysis on what I called a "plausible implementation strategy" for each device. In this scenario, a PICC device is inserted at the bedside or basic procedure room, by two nurses, using ECG to guide line placement. The insertion of a HICK and PORT device is undertaken by at least two nurses, in a basic procedure room, using ECG to guide line placement. This model for service delivery of a HICK and PORT is standard practice within The Christie NHS Foundation in Manchester, UK. Basing my Value of Implementation analysis on this model of care provided decision-makers with evidence which was not limited by the heterogeneity of service delivery and cost

observed in the CAVA trial. This meant that they were better positioned to plan for a PORT service based on a feasible and cost-effective model of service delivery.

The Value of Implementation framework required us to choose a single measure to represent the value of the health technology. This is typically captured in the quality adjusted life year (QALY) measure, based on the health-related quality of life questionnaire EQ-5D (EuroQol). However, the QALY is limited in the context evaluating medical devices. The hypothesised benefit of PORT, in terms of a reduction in complication rate, was the primary purpose of the CAVA clinical trial (203). Fewer complications, and the associated reduced disruption to anti-cancer therapy, is the primary benefit to patients of receiving a PORT device. Infection is a common and potentially serious complication associated with VADs. For this reason, I chose to use the difference in infection rate associated with a PORT, compared with HICK or PICC, as the measure of benefit used in the Value of Implementation framework.

To determine the potential cost-effectiveness of a PORT service, using the Value of Implementation framework, I needed to identify several parameters. Firstly, the eligible population to which the health technology will apply. Secondly, any additional "fixed" costs, such as training or setup costs, not included within the "variable" cost of providing the health technology to each patient. Finally, I needed the expected net monetary benefit per patient receiving a PORT. The NMB is comprised of the expected per patient monetised benefit of receiving a PORT – that is, the reduction in infection rate multiplied by a willingness-to-pay for this reduction, minus the cost of providing the PORT. There is no validated or established value for a willingness-to pay to avoid infections in this patient population. Furthermore, given the range of potential complications possible - from the VAD requiring a simple catheter"flush" to pulmonary embolism or infection -, and the associated consequences of these complications, defining a single average willingness-to-pay to avoid a complication for this population is not straightforward. However, given that infection is a common and potentially serious complication associated with the use of a VAD, I believe that adopting the

financial consequences of infection as a willingness-to-pay for avoding infection was a reasonable proxy.

Based on a WTP of £16,095, my Value of Implementation analysis found that PORT was likely to be worth up to £24 million, compared with HICK, and up to £800,000, compared with PICC, to the NHS over five years. My sensitivity analysis showed that, even at a willingness to pay of £0, PORT was still likely to be cost-effective, compared with HICK, due to PORT's lower cost per patient. Compared with PICC, the threshold at which a PORT service was likely to be considered cost-effective was at a willingness-to-pay to avoid infection of approximately £10,500 per infection avoided. These results suggest that, compared with HICK, PORT is very likely to be considered a cost-effective device option. Compared with PICC, PORT may be considered a cost-effective option. Whether or not it is will depend on what the NHS is willing to pay to avoid an infection in this patient population.

The difference in the infection rate between PORT and PICC or HICK was used to capture the benefit associated with PORT in the Value of Implementation analysis. However, my cost-consequence analysis included multiple outcomes which are important to patients and decision-makers which could have been used in the analysis. At present, the Value of Implementation framework is limited in its ability to consider only a single outcome of interest (typically, QALYs). To undertake a more holistic assessment of the value of a venous access device, a patient and public involvement exercise could have been undertaken to identify a range of outcomes relevant to patients and decision-makers for inclusion within the CAVA trial. Given these outcomes, we could have estimated a "treatment effect" for each outcome, by venous access device received (as I did in my cost-consequence analysis). A multi-criteria decision analysis (MCDA) could then have been undertaken with patients and decision-makers to explicitly trade-off (e.g., via "weighting") the importance each participant places on each outcome of interest. A recent methodological paper proposed a similar approach. Network meta-analysis was used to identify multiple outcomes across multiple

treatment options. MCDA was then used to identify the optimal treatment selection in the context where multiple outcomes are relevant (211).

I also could have used discrete choice experiments to determine the weightings for each outcome of interest, including cost, thus allowing us to make cost-effectiveness recommendations. This would have allowed us to make a recommendation for the choice of venous access device, explicitly informed by patients' and decision-makers' preferences across the entire range of relevant clinical outcomes. This would have had the advantage of demonstrating the willingness-to-pay of patients for these outcomes, specific to this patient population. A disadvantage of this approach would be that this WTP estimate would not be comparable with those developed on the general population, as recommended for use in economic evaluation in the UK.

The Value of Implementation framework is well designed to consider the cost-effectiveness of improved implementation, based on a cost-per-QALY framework. However, as I have discussed, the cost-per-QALY metric may provide a narrow perspective regarding what patients value, particularly in the context of complex interventions. Therefore, further research into how Value of Implementation methods could capture additional domains of value, and how these attributes may be traded-off against one another, may help improve decision making in this area.

In addition, further work could examine how best to incorporate implementation into other methodological frameworks suitable for economic evaluation. Implementation, and the costs and benefits associated with it, could be incorporated into the range of outcomes considered within a MCDA. The ability of MCDA to trade off a range of competing outcomes means that, compared with the Value of Implementation framework, it may be particularly well suited for the valuation of complex interventions.

The choice of method used to assess the issue of implementation, in the context of a complex intervention, will likely depend on the health technology in question. In the case of mechanical thrombectomy, the traditional methods used to assess the value of this technology – a within trial analysis and lifetime analysis, based on a cost-per-QALY metric - were limited. However, they were limited largely due to the absence of implementation costs associated with the set up and delivery of thrombectomy. The benefits of thrombectomy are arguably well captured within the QALY metric. In this context, the Value of Implementation framework (used in Chapter 4) which compared the population benefit (based on the QALY) with the population cost (including implementation cost) may be sufficient, since all the relevant costs and benefits associated with the technology can be captured within this framework. However, in the context of venous access devices for anti-cancer therapy, while the additional implementation costs of PORT could be captured using the cost-per-QALY framework, the benefits of a PORT were not well captured within the QALY metric. As such, a MCDA which can incorporate and trade-off a broader range of outcomes may have been more appropriate.

More generally, if the costs and benefits of a technologies can be captured within the "cost" and "QALY" metric, then the Value of Implementation framework, which is based on a cost-per-QALY approach, may be sufficient. However, if the costs and benefits of the technology cannot be captured within the cost or QALY metric, then more holistic methods may be more suitable.

The reliability of resource use data in the CAVA trial was an issue. The trial captured resource use data on device insertion and unplanned inpatient and outpatient visits during follow up. The trial resource use questionnaire specified that the inpatient and outpatient visits should relate directly to device complications. However, it is not clear if this instruction was strictly followed during data capture. For example, there was a patient randomised to a PORT who spent 54 days in hospital during follow-up. Clinicians involved in the trial subsequently advised that this was very unlikely to be related to the venous access device they received.

Conversations with the trail team highlighted that inpatient and outpatient resource use follow-up data were particularly not well captured within the trial. Without data recording the reason for each inpatient and outpatient visit, I cannot be sure to what extent these visits were a direct result of device complications or due to other reasons also.

The CAVA trial did not capture data on device replacement following a complication. This would include both the cost of the device itself, alongside the time of clinicians required for insertion. The CAVA trial also did not capture resource use relating to several additional costs which are likely to be incurred in clinical practice. Specifically, the cost of regular device "flushing" and device insertion training and access training costs. However, if I had been able to engage with the trial team earlier in this project, I could have emphasised the importance of collecting data relating to resource use - such as follow-up visits and device replacement. I also could have explained how these data would be used in economic evaluation, and how these data would have allowed us to provide a more realistic assessment of the likely cost-effectiveness of PORT in the real-world setting. However, in the absence of such data, assumptions and modelling allowed us to address this issue. I incorporated data relating to device flushing (undertaken at home by a nurse), device insertion and access training costs, and device replacement cost into the Value of Implementation analysis, allowing us to provide more realistic evidence on the potential cost-effectiveness of PORT in routine practice.

6.3.1 Reflections on the process of implementing mechanical thrombectomy in the UK

The MR CLEAN clinical trial was published in October 2014 and showed the superiority of mechanical thrombectomy, compared with standard of care, in the treatment of acute ischaemic stroke (155). In 2015 the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) trial was closed due to a lack of clinical equipoise (43).

During this time, thrombectomy was infrequently performed in Scotland. Those procedures which were performed typically took place at the Western General Hospital, NHS Lothian. In 2018, this service was suspended, and no thrombectomies were undertaken in Scotland. The main reason cited for this was a "lack of resources". NHS Scotland's National Planning Board subsequently commissioned the Thrombectomy Advisory Group (TAG) to develop a business case to consider the introduction of 24/7 thrombectomy across Scotland.

In 2020, the Scottish Government announced plans for a national thrombectomy service with the capacity to treat around 800 stroke patients each year. The Scottish Government originally allocated £12.5 million for a thrombectomy service in 2022. However, this investment was reduced to £7.9m in the Emergency Budget Review in November 2022. Following campaigning from clinicians and stroke charities, the Scottish Government announced on 16th December 2022 that they would reserve their planned cut in investment in a thrombectomy service. Currently, the plan is for a 24/7 thrombectomy service at three sites around Scotland – Glasgow, Edinburgh, and Dundee. As of February 2023, patients access to mechanical thrombectomy in both Scotland and UK is still lacking. Financial pressures are the most commonly cited reason for this. However, as my case study demonstrated, it is not necessary to achieve full implementation to realise the benefits of thrombectomy. In the case of Scotland, focusing implementation on a large population centre (and hence greater eligible population), such as Glasgow or Edinburgh, may allow the partial implementation of thrombectomy, where the greatest QALY gain could be achieved, without the financial implementation of a full nationwide service.

In June 2019 I attended a "Preparing for Thrombectomy in Scotland" workshop in Stirling, hosted by the Thrombectomy Advisory Group (TAG). This brought together healthcare decision-makers within the Scottish Government with senior stroke consultants (including representatives from St. Georges University Hospital in London where a 24-hour service is already established). My own impression of the workshop was one of surprise at the absence of any discussion regarding the potential cost-effectiveness for mechanical thrombectomy in the real-world setting. While financial challenges and service feasibility were a major discussion point, the value of a service, and of alternative modes of delivering a service, played no role whatsoever in the discussion. My impression was of a decision-making process which first decides upon whether or not a health technology is clinically effective, and then if it is deemed so, the cost and feasibility of implementing the service.

However, in the case of mechanical thrombectomy, it was not clear from the clinical trial evidence and subsequent cost-effectiveness analyses exactly how this technology would be implemented, where and for whom. Without this knowledge, it was simply not possible to say whether or not mechanical thrombectomy was likely to be cost-effective in routine practice. This lack of discussion of cost-effectiveness may be a reflection of the fact that medical devices in the UK, unlike pharmacological interventions, are not subject to a formal decision-making process whereby the value of the intervention is assessed. The establishment of such processes would allow for a more consistent and transparent approach to decision making, in the context of medical devices and complex interventions.

6.3.2 Reflections on the process of implementing a Port service in the UK

Following publication of the CAVA clinical trial (203), The Beatson West of Scotland Cancer Centre revised their indication for a PORT for a planned length of treatment from six to three months or greater (personal communication). NHS Lothian have also incorporated PORT, alongside HICK and PICC, among their suite of venous access device options available to patients. Again, personal communication with a senior oncologist within NHS Lothian suggested that the publication of the CAVA trial was instrumental in this decision.

However, broadly speaking, implementation of a PORT service throughout the UK has been disappointing. The CAVA trial team recently reached out to Health Improvement Scotland (HIS) to request support for an evidence review from the Evidence Directorate. However, this request was declined. HIP stated that *"although there appears to be new (and positive) evidence around the technology, the technology is not new and the wider buy-in to the issue was not demonstrated. In light of immediate national resource and clinical pressures, the triage team also noted the potential for additional cost and service pressure (e.g., training requirements) to an already under pressure NHS Scotland."* It was disappointing that "buy-in" was cited as a reason to not consider our application further. To achieve buy-in, we will need to promote the clinical- and cost-effectiveness of PORT. An evidence review supported by HIP is one way in which we believe this could have been achieved. However, it is clear that the implementation of any health technology which involves an additional cost to the NHS, even if it is cost-effective, is likely to be challenging given the current economic and health burden on the service.

The CAVA trial was published in July 2021. This was a time when COVID-19 – related lockdowns and other measures to limit social contact were intermittently being enforced. This limited the ability of the study co-authors to actively engage with patients and stakeholders in the normal manner, for example via presentations at clinical conferences. This may have had a negative impact on the implementation of the study findings. However, the CAVA study was a large clinical trial, conducted in an area where there was hitherto a

lack of clear evidence, and the results were published in a reputable journal. This highlights the point that the publication of research evidence in not always sufficient to change clinical practice (19). In some cases, active effort is required. Providing the evidence necessary to change clinical practice requires a careful consideration of the full costs and benefits of a health technology. For this reason, health economists are particularly well placed to play a leading role in this area. In the case of CAVA, our next step is to engage with the Scottish Government and the Scottish Intercollegiate Guideline Network (SIGN) group to encourage the recommendation of PORT in Scottish clinical guidelines. In March 2023, the principal investigator Jon Moss and I will present the results of the CAVA trial at the 6th annual Scottish Cancer Clinical Research Conference. A key focus of our talk will be on how we can promote the implementation of a PORT service into routine practice within the UK, given the CAVA trial results and results of the economic evaluation outlined in this thesis.

6.4 Areas for further research

The use of economic evaluation alongside implementation science is a growing area of methodological interest. Reeves et al. (2019) undertook a review of studies evaluating the costs and consequences of strategies directed towards enhancing the implementation of public health interventions (212). Just 14 studies were identified between the period of 1990 and 2017. They found that the methodological quality of these studies varied significantly and that there was no evidence of an improvement over time. Roberts et al. (2019) undertook a review of health economic methods applied in the field of implementation science (39). Similarly, they found that the quality of the studies was mixed, and that the use of such methods was not common. Dopp et al, (2019) recommends that implementation scientists begin to develop a research agenda around mixed-method economic evaluation (46). They show how qualitative data can be used enrich quantitative economic evaluation, by complementing each item in the widely used Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist with contextual insights gained from qualitative analysis. Based on the results of their review, Reeves et al. (2019) also proposed a checklist of reporting standards and recommendations, to be used alongside the Drummond and CHEERS checklist, to improve the quality of economic evaluations of implementation studies.

The Standards for Reporting Implementation Studies (StaRI) checklist provides a standardised process for reporting studies evaluating implementation strategies (213). Similar to the CHEERS checklist for economic evaluation (214), the StaRI checklist encourages users to document the details of the methods involved in their evaluation. However, details on the justification for economic evaluation methods used (e.g., CCA, CBA, CUA, CEA), the handling of uncertainty, and evaluation perspective (e.g., healthcare system, societal) used could further improve the quality of implementation studies. Importantly, this checklist distinguishes between intervention costs and implementation costs. However, it fails to distinguish between the various elements of the implementation process (e.g., planning, scaling up, and sustainment) (215). Finally, alongside a justification of economic evaluation method used, the checklist could be strengthened by including an item in the discussion

section on how final health economic outcomes (e.g., cost-per-QALY, cost per increase in uptake, etc.) should be interpreted and how (if at all) they may be traded-off against one another. In this context of a cost-per-QALY analysis, with a known willingness-to-pay threshold, this is clear. However, how to value and trade-off the outcomes of other forms of economic evaluation is less obvious and would benefit from further exploration in the discussion of an implementation study.

The field of implementation science similarly has a range of tools and checklist which are designed to assist in the implementation process. Noting this, the Consolidated Framework for Implementation Research (CFIR) was developed to combine and standardise framework for implementing research findings in practice (25). A useful next step within the context of HTA may be for the development of a consolidated framework for incorporating implementation within the economic evaluation of health technologies. O'Leary et al. (2022) have demonstrated one way in which this might be achieved, by applying a range of existing methods for data collection and analysis, relevant from a health economic perspective, within the EPIS framework (125, 126). However, it may be that the challenge of implementation is too contextual to be realistically combined in a single framework. If so, consistent guidance which explains how, where and when current methods should be utilised in the development, evaluation and implementation of a health technology may be more suitable.

Krebs et al. (2021) outline six key areas of methodological development required to enhance the uptake and impact of cost-effectiveness analysis in implementation research (215). Among these are suggestions for ways in which we can better estimate the potential reach of health technologies and more accurately capture and measure data relating to uptake at each stage of the implementation process. The authors also highlight the need to generate cost data which are more detailed, in terms of which stage of implementation it relates to, and which takes into account the likely functional form of the cost process, allowing

consideration of the potential for increasing or decreasing returns to scale from implementation.

The traditional research pipeline typically follows a linear, staged process from efficacy to effectiveness to implementation. The siloed evaluation of each aspect of a heath technology may contribute to the delay we see in translating research findings into clinical practice (152). Hybrid approaches to the evaluation of health technologies - so called "effectiveness-implementation" studies – offer an alternative to the traditional approach (152, 216). This type of study may focus primarily on testing efficacy, while gathering data on implementation. An example of this would be a process evaluation alongside a randomised controlled trial. Implementation data gathered at this stage are likely to include barrier and facilitators to implementation. Alternatively, a hybrid approach may focus on testing implementation strategies, while gathering efficacy data, such as patient acceptability, as a secondary outcome. Finally, the study may focus on the dual testing of implementation strategy and efficacy outcomes. This approach moves beyond simple barriers and facilitators and requires the identification of an explicit implementation strategy which is measurable, for example, in terms of fidelity or adoption. Both efficacy and implementation strategy are then tested simultaneously within the trial. The World Health Organisation's practical guide to implementation research in health advocates for the use of effectiveness-implementation hybrid trials as a more effective means of translating researching findings in practice (217). Building economic evaluation methods into an effectiveness-implementation hybrid study could further assist decision-makers in considering the real-world applicability of research findings.

The use of conceptual modelling to justify the design of health economic models is recommended by NICE. A review and guidance on the use of conceptual modelling in healthcare is provided by McMeekin et al. (218, 219). Hinde et al. (2020) highlight the importance of conceptual modelling specifically as it relates to the economic evaluation of implementation (220). Economists usually regard set-up costs as "sunk costs" because they

do not affect the cost of treating the next patient – i.e., the marginal cost. However, implementation is typically undertaken in stages. As such, the stage of implementation defines the margin. For example, if a completely new technology is being introduced into a healthcare system, then the healthcare system is the margin, and the set-up (or capital) costs are the marginal costs and should arguably be included in an economic evaluation of a health technology. However, these costs are routinely regarded as sunk costs and omitted from analysis. If instead the goal is to increase the number of patients receiving an established technology, the margin is the next patient, and the marginal cost is the cost of treating the next patient. These costs, in contrast, would typically be included within an economic evaluation. As such, each phase of implementation represents a different decision margin for economic evaluation. The same principal applies to implementation outcomes, which may be measured at the patient, health board or national level. For these reasons, it is necessary to be explicit regarding the perspective, cost and outcomes relevant at each stage of analysis. This can be mapped out in a conceptual model which can be used to both engage with stakeholders and guide analysis. In my own case studies, I found conceptual models to be a valuable tool for engaging with clinicians and other stakeholders. This was particularly relevant for my second case study, where we had to consider a greater range of costs and outcomes associated with the use of a venous access device. The conceptual model allowed us to illustrate the pathway by which clinical outcomes were experienced, and costs accrued, depending on the choice of VAD, and how this had the potential to change depending on how the device was implemented (i.e., via a nurse-led or radiology-led model of care).

The costing of healthcare resource use for health technology assessment typically involves attaching unit costs to resource use items – such as drugs, staff, and setting. While this also often applies to costing implementation, the costs associated with implementation are often more “activity-driven” (221) and less tangible. This may include formal and informal activities, some of which may be undocumented. From my own personal experience, this was certainty true of both case studies included in this thesis. Guidance is available on the measurement and inclusion of specific cost components, given the decision-makers’

perspective (17). However, a more structured and pre-planned approach to implementation would help to ensure that all relevant cost items are identified and captured for evaluative purposes.

A review of the use of economic evaluation methods in implementation studies found that only one third of studies reported details of how parameter uncertainty was accounted for in their study (39). The use of one-way (OWSA) and probabilistic sensitivity analysis (PSA) is common within the economic evaluation of health technologies. While these techniques are useful in the economic evaluation of implementation, it is likely that other techniques, such as scenarios analysis to model the impact of alternative implementation strategies, will be valuable and worthy of further development. In the second case study of this thesis, a PSA would not have illustrated the key uncertainties associated with whether or not a PORT service would be cost-effective in clinical practice. Rather, it was the consideration of a nurse-led scenario for the delivery of a PORT service which allowed me to suggest that PORT could be cost-effective when delivered in routine clinical practice.

Health economists seeking to foster implementation need to consider the wider financial landscape in which a healthcare system is operating (222). The NICE guidance for technology appraisal recommends the use of a cost-per-QALY approach, in which all cost-effective health technologies are theoretically suitable for implementation. However, local health boards typically face an annual budget in which decision-maker need to consider which technologies are financially affordable. In this context, budget impact, return on investment and programme budget marginal analysis may be more relevant (131). This is a challenge which was apparent in the implementation of both technologies highlighted in the case studies of this thesis.

Health economists already have a wide range of tools which can contribute to the study of implementation. The cost-utility (CUA) framework can be used to estimate the value of implementation, in terms of the population-level net monetary benefit gain (4). Cost-benefit

(CBA) and cost-consequence (CCA) analysis have the benefit of being able to incorporate a broad range of health and non-health costs and benefits across different sectors (30). In the context of an implementation study, measures such as fidelity score or rate of uptake are often used. These measures could conveniently be incorporated in a cost-effectiveness analysis (CEA), measuring, for instance, the cost per increase in rate of uptake (46).

The use of a common outcome measure would help to facilitate the incorporation of implementation within economic evaluation. Where an increase in uptake translates into an increase in QALYs, comparisons could be made across implementation strategies and disease areas. However, where the benefits of increasing uptake are not well captured within the QALY, comparison beyond a single disease area or decision problem may not be possible. Further research should aim to identify which outcomes, relevant from an implementation perspective, can be used in economic evaluation in a way which allows comparability across disease areas. The next step would then be to determine a willingness-to-pay for improvements in these outcomes.

Any of the four standard methods of economic evaluation (i.e., CUA, CBA, CCA, CEA) can be informed by a broader suite of tools which are particularly relevant to the challenge of implementation. For example, discrete event simulations (DES) and agent-based models (ABM). These models are able to capture patient attributes (e.g., time to event, patient characteristics at the event, etc.) and also cost and outcome (e.g., QALYs gained, complications avoided, etc.) estimates over time. Of particular relevance to implementation, patients are able to interact with other entities (resources) within the model (e.g., doctors, time-to-treatment, appointment slots, equipment, etc.). Interactions can be delayed if we specify that one event can only occur following another event, or if an event can only take place once certain resources become available. This allows one to model, for instance, the impact of service capacity via the formation of queues and the potential for patients not to receive care in a pre-specified time period. Agent based models are similar to DES but differ in one important concept: the autonomy of the individual agent (e.g., patient, doctor, etc.)

within the model. In a DES, patients simply flow through the model, akin to water flowing through a pipe. However, in ABMs patients can be programmed to exhibit their own individual behaviours. In a DES, patients may be faced with a service constraint which delays the occurrence of future events. In this situation, the patient has no choice but to wait until a resource becomes available. In an ABM, a patient can react to a constraint. For example, faced with delays or queuing for treatment at a local hospital, the agent can choose to attend an alternative hospital. This sort of flexibility has the potential to make cost-effectiveness models more relevant to a real-world setting.

However, while more advanced modelling methods such as DES and ABM may enrich our evaluations, they come with the additional cost of time and coding complexity. In a systematic review, Stanfield et al. (2014) identified two empirical economic evaluations which compared the use of Markov modelling with DES (223). In one study, Simpson et al. (2009) found that while a Markov model was associated with less computation burden, a DES represented the course of disease more naturally with fewer restrictions, giving the model greater face validity (224). However, the overall cost-effectiveness estimates produced by a Markov model and DES were similar, suggesting that the additional computational burden may not have been justified in this case. Another study identified in the review, Karnon et al. (2003), reported a similar experience (225). The DES approach allowed a more realistic and accurate representation of the data, which had to be balanced against the additional computational time. The authors suggested that the DES approach would be justified in situations where the increased flexibility of this approach would apply to a significant proportion of the model. In the context of their empirical study, in the area of early breast cancer, they found that the similarity in cost-effectiveness ratios meant that the use of an alternative modelling approach was unlikely to change the reimbursement decision. Therefore, in this example, a Markov modelling approach would be sufficient, since the additional benefits, in terms of realism and flexibility, would not outweigh the additional costs, in terms of development and computational time. In concluding their review, Stanfield et al. (2014) suggest that DES may be superior to Markov modelling where supply shortages

and subsequent queuing, or diversion of patients via different clinical pathways in the healthcare system, are likely to be a significant driver of cost-effectiveness. Models that can capture this heterogeneity across patients and settings are particularly well positioned to enrich an economic evaluation with the sort of contextual factors and complexity required to incorporate implementation (215). The issue of when and how these methods should be deployed, such that the benefits of increased complexity exceed the computation burden, is a topic which requires further research. However, early engagement with stakeholders within the assessment of health technologies would allow researchers to identify what the major barriers to implementation were likely to be. With this knowledge, researchers would be better placed to gather the correct data and plan for the most appropriate analysis required to answer the relevant research questions.

Knocke (2022) quite rightly highlight the fact that incorporating economic evaluation alongside implementation is "*appreciatively difficult and made worse by the lack of guidance for researchers*." (222) However, it is clear from the reviews, case studies and discussion in this thesis that progress is being made in this area – both in the context of increasing awareness of the issue of implementation and in beginning to generate guidance for researchers. To build on this progress, health economists and implementation scientists could benefit from developing a common language and set of tools which highlight the strengths (and weaknesses) of their respective disciplines. Both the fields of economic evaluation and implementation science are well developed in their own right. It is important that researchers working in their respective fields do not seek to "reinvent the wheel". Both disciplines should learn from one another and develop a set of tools which incorporate the strengths of one another's methods. While the reviews in this thesis have demonstrated that methods to incorporate implementation within the economic evaluation of a health technology are available, they are uncommonly and inconsistently applied in practice. The conceptual model presented Chapter 3 may provide a first step in developing guidance on how and where these methods are applied in health technology assessments.

A clearer signal from funders and reimbursement agencies on the need to consider implementation, and the development of decision makings structures to ensure this sort of evidence was used in practice, would encourage researchers to utilised, and develop further, the methods necessary to fully incorporate implementation within the economic evaluation of health technologies.

From my own perspective, building on the lessons I have learned, and the methods I have discovered over the course of my PhD, it is my hope that I can take the next step of providing a set of guidance for researchers attempting to bring implementation issues into their economic evaluations. To make sure that any proposed guidance is both relevant and practical, I plan to establish an "implementation within economic evaluation" working group, comprising of researchers, decision-makers and funders who are interested and experienced in this topic. I have begun work on this task have received declarations of interest from several researchers and decision-makers working in this area already. I envisage that the final proposed guidance with take the form of an extension to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist which will incorporate issues relating to implementation. Similar work, on different topics (e.g. surrogate outcomes, natural experiments) have adopted a similar approach (226, 227). Alongside the checklist, our guidance will also signpost researchers to the range of methods currently available for incorporating implementation within economic evaluation identified in Chapter 3 of this thesis. We will also develop further the conceptual model presented in Chapter 3 to signpost where the available methods may be most applicable in the process of developing and evaluating a health technology.

6.5 Implications for policy

The body of work contained within this thesis has demonstrated that methods for the incorporation of implementation within the economic evaluation of health technologies are available and continue to be developed. However, there is a lack of consistency in how, and if, these methods are applied in practice. My case studies have demonstrated the value of considering implementation, in terms of a more realistic evaluation of the potential cost-effectiveness of health technologies in routine clinical practice.

Given the availability of methods, and the benefit of using these methods to enrich our development and evaluation of health technologies, it could be considered surprising that these methods are not more commonly used. There are several reasons why this may be the case. Firstly, and most obviously, implementation has traditionally been considered beyond the remit of HTA researchers. As such, research projects do not typically plan or budget for implementation research. Another reason may be the perceived lack of demand from funding and reimbursement agencies. The NIHR's HTA programme does not explicitly fund implementation research. However, as the review presented in this thesis shows, implementation is being considered within evaluations funded by the programme. The NIHR's Health and Social Care Delivery programme does fund implementation research. However, this research tends to focus on quality and service improvement, rather than health technologies in a clinical setting.

There are several reasons which may explain why funders and reimbursement agencies do not explicitly recommend the use of implementation within the evaluation of health technologies. Firstly, agencies such as NICE and SMC have traditionally been tasked with assessing pharmacological interventions. However, in recent years we have seen an increase in the development of complex interventions, including multiple stakeholders, medical devices and diagnostics. As a result, implementation is becoming more relevant to HTA. When considering complex interventions, it is particularly important to consider how these technologies would be used in routine clinical practice. Secondly, because non-

pharmacological technologies do not follow the market access pathway of technologies requiring reimbursement guidance, the issue of implementation is typically considered the remit of local health care decision-makers. Where a new technology requires significant capital investment for implementation, national government may also play a role. For these reasons, implementation is often considered following, rather than as part of, the evaluation of a complex intervention.

Neither the National Institute for Health and Care Excellence (NICE) nor Scottish Medicines Consortium (SMC) are responsible for implementing health technologies. Rather, this is typically undertaken by local decision-makers (e.g., at the health board level). This may partly explain why implementation is not routinely incorporated in health technologies assessments submitted to NICE and SMC.

The decision-making process also varies throughout the UK. The NHS have a legal requirement to make funding available for heath technologies in England and Wales within 90 days of a NICE recommendation. While NICE do evaluate medical devices and diagnostics, they do not make legally binding reimbursement recommendations. In Scotland, the Scottish Medicines Consortium provide guidance on the value of health technologies (pharmacological technologies only), however, their recommendations are not legally binding. The assessment of diagnostic and medical devices is the remit of the Scottish Health Technologies Group (SHTG). However, again, these recommendations are not legally binding. The myriad agencies involved in the decision-making process - from NICE and SMC to national and local budget holders – creates a barrier to the implementation of complex interventions in particular. However, while the legal requirement to provide pharmacological technologies may help to facilitate implementation, the lack of legal requirement associated with non-pharmacological technologies should not be seen as the major barrier to implementation. Rather, challenges arise from the fact that implementing non-pharmacological technologies is typically the remit of local healthcare commissioning groups, funded from a separate healthcare budget. This contributes towards the so called “post-code

lottery" of access to some health technologies, which is exactly the problem national reimbursement agencies were designed to address.

Given the financial pressures facing national health care systems, the landscape for implementing new health technologies is becoming more challenging – particularly for complex interventions which require addition set-up costs or pathway reconfiguration. For this reason, the benefits of implementing cost-effective or cost-saving complex interventions should be considered over an appropriate time horizon and perspective. While the upfront costs associated with implementing a new technology may seem prohibitive, greater benefits may accrue over time or within other areas of the healthcare system. For example, the cost implications of implementing mechanical thrombectomy was recently assessed within a single hospital currently performing this procedure in the UK (228). They found a cost saving of £17,221 per patient for the hospital, based on the difference in bed days, additional investigations, and rehabilitation. This was achieving without any reimbursement for undertaking the procedure itself.

The identification of a clear pathway, and agency responsible, for the assessment and implementation of medical devices and diagnostics could improve access to these technologies. A more structured and transparent approach to decision making in this space would mean that, even in situations where the decision was taken not to implement (or not to increase implementation), the reasoning and evidence upon which these decisions were taken would be clearer and more consistent.

Both case studies included within my thesis were based on health technologies assessed in the UK. As such, it was necessary to consider implementation within the context of the UK healthcare system and decision-making processes. However, it is important to note that the fundamental challenges associated with the implementation of health technologies are likely to be relevant in the context of healthcare systems worldwide. World Health Organisation guidance on implementation recognises the important of considering the cost of

implementation, the value for money of implementation strategies, and the value of acquiring further research knowledge (Value of Information) (217). The challenges of implementation which are likely to be country-specific include the decision-making processes which are in place to consider implementation, whether or not the healthcare system is publicly or privately funded, and the type of evidence required by decision-makers in their context.

Sculpher et al. (1997) proposed an iterative approach to the economic evaluation of health technologies (229). Under this approach, economic evaluation is incorporated within the entire lifecycle of the development and evaluation of a health technology, from the basic science to the generalisation of study findings to routine clinical practice. In a similar vein, we should consider taking an iterative approach to the economic evaluation of implementation. We should begin to think about economic evaluation and implementation at the beginning of the design and evaluation of a health technology. The aim at this stage should be to consider how this technology will be used in routine clinical practice and any potential barriers to implementation. Close collaboration with stakeholders at an early stage can ensure that research studies are designed to gather evidence which is relevant to patients, clinicians and decision-makers. Implementation of a health technology is typically phased – it is rare that patients in all settings and locations are able to receive a health technology immediately. The staggered implementation of a health technology should be used as an opportunity to gather data on the real-world barriers and facilitators of implementation. Researchers and decision-makers can then assess and adapt how a technology is being implemented as to improve uptake.

As highlighted at the beginning of this thesis, the Department for Health and Social Care and the NHS have both identified the implementation of clinically effective and cost-effective health technologies as a key priority for the healthcare system (15, 16). The NIHR has also highlighted the need to develop new methodologies involving a range of disciplines, including implementation science, in the effort to improve access to novel health

technologies (230). Therefore, the time is apt for funders, reimbursement agencies, decision-makers and researchers to work together to develop guidance for those working in this area. Health research funders should consider whether implementation ought to play a greater role within the evaluation of complex interventions. Reimbursement agencies should consider if we need to develop formal process by which the issue of implementation can be considered alongside the more traditional mechanisms for assessing health technologies.

6.6 Conclusion

The aim of this thesis was to demonstrate the value of considering implementation within the economic evaluation of health technologies. My thesis began with a description of the issue of implementation as it relates to health technologies. I highlighted the reasons why many cost-effective health technologies often fail to achieve full implementation in routine clinical practice, the difference between the evaluation of health technologies and the evaluation of the implementation of health technologies, and the lack of clear guidance in this area.

My first literature review assessed how implementation has hitherto been addressed in health technologies assessments funded by the NIHR HTA programme in the UK. I showed that implementation is currently being considering within the HTA programme in an inconsistent and ad hoc manner. In addition, the issue of economic evaluation and implementation were typically considered in isolation – with implementation factors only considered after the economic evaluation had taken place. This finding was at odds with MRC guidance which advised that implementation should be considered in a cyclical manner, alongside the development, feasibility/piloting and evaluation of an intervention.

In my second literature review, I mapped out which methods are available for considering implementation alongside economic evaluation. The methods identified in the review could be categorised into four broad themes – i) policy cost-effectiveness approach, ii) Value of InformationValue of Implementation approach, iii) study design approach, and iv) costing of systems change approach. Across these four categories, I found that many methods are already available for considering implementation alongside economic evaluation. What is missing is guidance for how these methods should be utilised in the development and evaluation of health technologies. I used a conceptual model to show where the available methods may be most applicable within the lifecycle of the development and evaluation of a health technology.

In my first case study, I worked closely with stroke clinicians and stakeholders to understand the challenges of implementing mechanical thrombectomy in routine practice. This allowed me to incorporate additional costs not captured within the trial setting, ensuring that my research was addressing questions relevant to stakeholders and decision-makers in this area. Furthermore, I showed that the QALY benefit to the eligible population from mechanical thrombectomy was likely to exceed the cost of implementation if we can achieve at least 30% implementation across the UK. This additional evidence means that decision-makers were better able to plan for the resource requirements necessary to implement this technology in their own setting. It also demonstrated that it was not necessary to achieve full implementation to realise the benefits of mechanical thrombectomy.

In my second case study, I recognised that, in the context of a complex intervention where multiple outcomes may be relevant to multiple stakeholders, the applicability of the cost-per-QALY framework may have been limited in capturing the full value of a venous access device. For this reason, we undertook a cost-consequence analysis to evaluate a range of clinical and economic outcomes relevant to patients and decision-makers. This allowed patients and decision-makers to determine for themselves the importance they place on these outcomes when choosing an appropriate device. Recognising the heterogeneity in service delivery and cost within the CAVA trial, I worked alongside radiologists and nurses to develop a plausible scenario for the delivery of a PORT service in routine practice. I used the Value of Implementation framework to estimate the total value of implementation. I also then used this framework to answer additional questions related to implementation, such what is the value of delivering PORT to just 50% of patients requiring a VAD? What is the minimum willingness to pay for infections avoided for the benefits of PORT to exceed the cost of implementation?

My case studies allowed me to highlight the limitations of the cost-per-QALY approach in the context of complex interventions. In both case studies, I demonstrated how the Value of

Implementation framework can be adapted to allow researchers to answer questions which go beyond the cost-per-QALY metric and provide evidence which is more useful to decision-makers considering the implementation of complex interventions. They also allowed me to identify gaps in our current approach. For example, implementation is too often considered retrospectively, and on an ad hoc basis. Additional methods which explicitly incorporate implementation and economic evaluation alongside one another may be required. However, we already have sufficient methods to make progress in this area. What is missing is practical and consistent guidance on where, when, and how available methods can be incorporated in the development, evaluation, and implementation of a health technology.

References

1. Walker SM FR, Palmer SJ, Sculpher M. Getting cost-effective technologies into practice: the value of implementation. Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU). 2014.
2. Mason J, Freemantle N, Nazareth I, et al. When is it cost-effective to change the behavior of health professionals? JAMA. 2001;286(23):2988-92.
3. Claxton K. Bayesian approaches to the Value of Information: implications for the regulation of new pharmaceuticals. Health Econ. 1999;8(3):269-74.
4. Walker S FR, Whyte S, Dixon S, Palmer S, Sculpher M. Getting cost-effective technologies into practice: the value of implementation. Report on framework for valuing implementation initiatives. Policy Research Unit in Economic Evaluation of Health and Care Interventions. Universities of Sheffield & York; EEPRU Research Report 024. Policy paper/document 01/08/2014. 2014.
5. Fenwick E, Claxton K, Sculpher M. The value of implementation and the Value of Information: combined and uneven development. Medical decision making : an international journal of the Society for Medical Decision Making. 2008;28(1):21-32.
6. Guthrie S, Hafner M, Bienkowska-Gibbs T, et al. Returns on research funded under the NIHR Health Technology Assessment (HTA) Programme: Economic analysis and case studies. Santa Monica, CA: RAND Corporation; 2015.
7. Green LW, Ottoson JM, García C, et al. Diffusion theory and knowledge dissemination, utilization, and integration in public health. Annu Rev Public Health. 2009;30:151-74.
8. Balas EA, Boren SA. Managing Clinical Knowledge for Health Care Improvement. Yearb Med Inform. 2000(1):65-70.
9. Grant J, Green L, Mason B. Basic research and health: a reassessment of the scientific basis for the support of biomedical science. Research Evaluation. 2003;12(3):217-24.
10. Wratschko K. Empirical Setting: The pharmaceutical industry. In: Wratschko K, editor. Strategic Orientation and Alliance Portfolio Configuration: The Interdependence of Strategy and Alliance Portfolio Management. Wiesbaden: Gabler; 2009. p. 87-96.
11. Westfall JM, Mold J, Fagnan L. Practice-based research--"Blue Highways" on the NIH roadmap. Jama. 2007;297(4):403-6.
12. Bauer MS, Damschroder L, Hagedorn H, et al. An introduction to implementation science for the non-specialist. BMC Psychology. 2015;3(1):32.
13. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med. 2011;104(12):510-20.
14. Ubbink DT, Guyatt GH, Vermeulen H. Framework of policy recommendations for implementation of evidence-based practice: a systematic scoping review. BMJ Open. 2013;3(1):e001881.
15. Care DoHaS. Accelerating access to treatments and services is being improved so that more patients can benefit. Available at https://www.england.nhs.uk/aac/2019/05/09/accelerating-access-to-treatments-and-services-is-being-improved-so-that-more-patients-can-benefit/. Accessed on 5th January 2023.

16. Care DfHaS. Department for Health and Social Care's areas of research interest. Available at https://www.gov.uk/government/publications/department-of-health-areas-of-research-interest/department-of-health-areas-of-research-interest. Accessed on 1st February 2023.
17. Gold HT, McDermott C, Hoomans T, et al. Cost data in implementation science: categories and approaches to costing. Implementation Science. 2022;17(1):11.
18. Ioannidis JPA. Why Most Clinical Research Is Not Useful. PLOS Medicine. 2016;13(6):e1002049.
19. Wallace J. Lost in translation: transferring knowledge from research to clinical practice. Advances in Psychiatric Treatment. 2013;19(4):250-8.
20. Moore GF, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. bmj. 2015;350.
21. Best SH, K. Gul, H. Ryder, T. Rapport, F. Hibbert, P., Smith A. Does implementation science have an implementation problem? Workshop report from the Evidence and Impact Summit 2021. . 2021;Available at https://www.mq.edu.au/__data/assets/pdf_file/0011/1178435/EIS-Report-Final-20210719-website.pdf. Accessed on 8th January 2023.
22. Skolarus TA, Lehmann T, Tabak RG, et al. Assessing citation networks for dissemination and implementation research frameworks. Implementation Science. 2017;12(1):97.
23. Graham ID, Logan J, Harrison MB, et al. Lost in knowledge translation: time for a map? J Contin Educ Health Prof. 2006;26(1):13-24.
24. Greenhalgh T, Robert G, Macfarlane F, et al. Diffusion of innovations in service organizations: systematic review and recommendations. The Milbank quarterly. 2004;82(4):581-629.
25. Damschroder LJ, Aron DC, Keith RE, et al. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implementation Science. 2009;4(1):50.
26. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health. 1999;89(9):1322-7.
27. Glasgow RE, Harden SM, Gaglio B, et al. RE-AIM Planning and Evaluation Framework: Adapting to New Science and Practice With a 20-Year Review. Frontiers in Public Health. 2019;7.
28. King DK, Shoup JA, Raebel MA, et al. Planning for Implementation Success Using RE-AIM and CFIR Frameworks: A Qualitative Study. Front Public Health. 2020;8:59.
29. Moullin JC, Dickson KS, Stadnick NA, et al. Ten recommendations for using implementation frameworks in research and practice. Implementation Science Communications. 2020;1(1):42.
30. Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ. 2021;374:n2061.

31. National Institute for H, Care E. Interim Methods Guide for Developing Service Guidance. Interim Methods Guide for Developing Service Guidance 2014. London: National Institute for Health and Care Excellence (NICE)
Copyright © 2014 National Institute for Health and Clinical Excellence, unless otherwise stated. All rights reserved.; 2014.
32. Eisman AB, Kilbourne AM, Dopp AR, et al. Economic evaluation in implementation science: Making the business case for implementation strategies. Psychiatry Research. 2020;283:112433.
33. (NICE) NIfHaCE. Health technology evaluations: the manual Accessed on 24th October 2022. Obtained from https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation 2022.
34. NICE. Developing NICE guidelines: the manual. Available at https://www.nice.org.uk/process/pmg20/chapter/introduction. Accessed on 10th May 2023. 2022.
35. Meacock R. Methods for the economic evaluation of changes to the organisation and delivery of health services: principal challenges and recommendations. Health Economics, Policy and Law. 2019;14(1):119-34.
36. Hoomans T, Severens JL. Economic evaluation of implementation strategies in health care. Implementation Science. 2014;9(1):168.
37. Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess. 2004;8(6):iii-iv, 1-72.
38. Hoomans T, Evers SM, Ament AJ, et al. The methodological quality of economic evaluations of guideline implementation into clinical practice: a systematic review of empiric studies. Value Health. 2007;10(4):305-16.
39. Roberts SLE, Healey A, Sevdalis N. Use of health economic evaluation in the implementation and improvement science fields—a systematic literature review. Implementation Science. 2019;14(1):72.
40. Powell BJ, Fernandez ME, Williams NJ, et al. Enhancing the Impact of Implementation Strategies in Healthcare: A Research Agenda. Front Public Health. 2019;7:3.
41. Cheung K, Duan N. Design of Implementation Studies for Quality Improvement Programs: An Effectiveness-Cost-Effectiveness Framework. Am J Public Health. 2014;104(1):E23-E30.
42. Willan AR, Eckermann S. Optimal clinical trial design using Value of Information methods with imperfect implementation. Health Econ. 2010;19(5):549-61.
43. Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry. 2017;88(1):38-44.
44. McGlynn EA, Asch SM, Adams J, et al. The Quality of Health Care Delivered to Adults in the United States. New England Journal of Medicine. 2003;348(26):2635-45.
45. Whyte S, Dixon S, Faria R, et al. Estimating the Cost-Effectiveness of Implementation: Is Sufficient Evidence Available? Value in Health. 2016;19(2):138-44.

46. Dopp AR, Mundey P, Beasley LO, et al. Mixed-method approaches to strengthen economic evaluations in implementation research. Implementation Science. 2019;14(1):2.
47. Petticrew M. When are complex interventions 'complex'? When are simple interventions 'simple'? European Journal of Public Health. 2011;21(4):397-8.
48. Moore GF, Evans RE, Hawkins J, et al. All interventions are complex, but some are more complex than others: using iCAT_SR to assess complexity. Cochrane Database of Systematic Reviews. 2017(7).
49. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655.
50. Craig P. Developing and evaluating complex interventions: current thinking (oral presentation). Economic Evaluation of Complex Interventions Symposium, Univeristy of Glasgow, 31st August 2017. 2017.
51. Dobbins M. Rapid Review Guidebook: steps for conducting a rapid review. Obtained on 24/5/2019. Available at https://www.nccmt.ca/uploads/media/media/0001/01/a816af720e4d587e13da6bb307df8c907a5dff9a.pdf. 2017.
52. Proctor EK, Powell BJ, Baumann AA, et al. Writing implementation research grant proposals: ten key ingredients. Implementation Science. 2012;7(1):96.
53. Neta G, Brownson RC, Chambers DA. Opportunities for Epidemiologists in Implementation Science: A Primer. Am J Epidemiol. 2018;187(5):899-910.
54. Burns KE, Duffett M, Kho ME, et al. A guide for the design and conduct of self-administered surveys of clinicians. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2008;179(3):245-52.
55. Management CfE-B. Critical Appraisal of a Cross-Sectional Study (Survey). Obtained on 18/09/2019. Available at http://www.cebma.org/wp-content/uploads/Critical-Appraisal-Questions-for-a-Cross-Sectional-Study-july-2014.pdf. 2014.
56. Popay J, Roberts H, Sowden A, et al. Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme Version. 2006;1:b92.
57. Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020;368:l6890.
58. Bonell C, Fletcher A, Fitzgerald-Yau N, et al. Initiating change locally in bullying and aggression through the school environment (INCLUSIVE): a pilot randomised controlled trial. Health Technology Assessment (Winchester, England). 2015;19(53):1-109, vii-viii.
59. Whitaker R, Hendry M, Aslam R, et al. Intervention Now to Eliminate Repeat Unintended Pregnancy in Teenagers (INTERUPT): a systematic review of intervention effectiveness and cost-effectiveness, and qualitative and realist synthesis of implementation factors and user engagement. Health Technology Assessment (Winchester, England).20(16):1-214.
60. Seguin M, Dodds C, Mugweni E, et al. Self-sampling kits to increase HIV testing among black Africans in the UK: the HAUS mixed-methods study. Health Technology Assessment (Winchester, England). 2018;22(22):1-158.

61. Francis NA, Gillespie D, White P, et al. C-reactive protein point-of-care testing for safely reducing antibiotics for acute exacerbations of chronic obstructive pulmonary disease: the PACE RCT. Health Technol Assess. 2020;24(15):1-108.
62. Richards SH, Campbell JL, Dickens C, et al. Enhanced psychological care in cardiac rehabilitation services for patients with new-onset depression: the CADENCE feasibility study and pilot RCT. Health Technology Assessment (Winchester, England).22(30):1-220.
63. Little P, Hobbs FD, Moore M, et al. PRImary care Streptococcal Management (PRISM) study: in vitro study, diagnostic cohorts and a pragmatic adaptive randomised controlled trial with nested qualitative study and cost-effectiveness study. Health Technology Assessment (Winchester, England).18(6):vii-xxv, 1-101.
64. Surr CA, Holloway I, Walwyn RE, et al. Dementia Care Mapping™ to reduce agitation in care home residents with dementia: the EPIC cluster RCT. Health Technol Assess. 2020;24(16):1-172.
65. Campbell F, Thokala P, Uttley LC, et al. Systematic review and modelling of the cost-effectiveness of cardiac magnetic resonance imaging compared with current existing testing pathways in ischaemic cardiomyopathy. Health Technology Assessment (Winchester, England).18(59):1-120.
66. Hood K, Nuttall J, Gillespie D, et al. Probiotics for Antibiotic-Associated Diarrhoea (PAAD): a prospective observational study of antibiotic-associated diarrhoea (including Clostridium difficile-associated diarrhoea) in care homes. Health Technology Assessment (Winchester, England).18(63):1-84.
67. Livingston G, Barber J, Rapaport P, et al. START (STrAtegies for RelaTives) study: a pragmatic randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of a manual-based coping strategy programme in promoting the mental health of carers of people with dementia. Health Technology Assessment (Winchester, England).18(61):1-242.
68. Freeman K, Connock M, Auguste P, et al. Clinical effectiveness and cost-effectiveness of use of therapeutic monitoring of tumour necrosis factor alpha (TNF-alpha) inhibitors [LISA-TRACKER enzyme-linked immunosorbent assay (ELISA) kits, TNF-alpha-Blocker ELISA kits and Promonitor ELISA kits] versus standard care in patients with Crohn's disease: systematic reviews and economic modelling. Health Technology Assessment (Winchester, England).20(83):1-288.
69. Guthrie S, Bienkowska-Gibbs T, Manville C, et al. The impact of the National Institute for Health and Care Research Health Technology Assessment programme, 2003-13: a multimethod evaluation. Health Technology Assessment (Winchester, England).19(67):1-291.
70. Michie S, Wood CE, Johnston M, et al. Behaviour change techniques: the development and evaluation of a taxonomic method for reporting and describing behaviour change interventions (a suite of five studies involving consensus methods, randomised controlled trials and analysis of qualitative data). Health Technology Assessment (Winchester, England).19(99):1-188.
71. Richardson R, Trepel D, Perry A, et al. Screening for psychological and mental health difficulties in young people who offend: a systematic review and decision model. Health Technology Assessment (Winchester, England).19(1):1-128.

72. Bailey JV, Webster R, Hunter R, et al. The Men's Safer Sex project: intervention development and feasibility randomised controlled trial of an interactive digital intervention to increase condom use in men. Health Technology Assessment (Winchester, England).20(91):1-124.
73. Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technology Assessment (Winchester, England).20(40):1-146.
74. Fortnum H, Ukoumunne OC, Hyde C, et al. A programme of studies including assessment of diagnostic accuracy of school hearing screening tests and a cost-effectiveness model of school entry hearing screening programmes. Health Technology Assessment (Winchester, England).20(36):1-178.
75. Jackson C, Dyson L, Bedford H, et al. UNderstanding uptake of Immunisations in TravellIng aNd Gypsy communities (UNITING): a qualitative interview study. Health Technology Assessment (Winchester, England).20(72):1-176.
76. Parry SW, Bamford C, Deary V, et al. Cognitive-behavioural therapy-based intervention to reduce fear of falling in older people: therapy development and randomised controlled trial - the Strategies for Increasing Independence, Confidence and Energy (STRIDE) study. Health Technology Assessment (Winchester, England).20(56):1-206.
77. Paton F, Wright K, Ayre N, et al. Improving outcomes for people in mental health crisis: a rapid synthesis of the evidence for available models of care. Health Technology Assessment (Winchester, England).20(3):1-162.
78. Tufail A, Kapetanakis VV, Salas-Vega S, et al. An observational study to assess if automated diabetic retinopathy image assessment software can replace one or more steps of manual imaging grading and to determine their cost-effectiveness. Health Technology Assessment (Winchester, England).20(92):1-72.
79. Birrell PJ, Pebody RG, Charlett A, et al. Real-time modelling of a pandemic influenza outbreak. Health Technology Assessment (Winchester, England).21(58):1-118.
80. Flowers P, Wu O, Lorimer K, et al. The clinical effectiveness of individual behaviour change interventions to reduce risky sexual behaviour after a negative human immunodeficiency virus test in men who have sex with men: systematic and realist reviews and intervention development. Health Technology Assessment (Winchester, England).21(5):1-164.
81. Melendez-Torres GJ, Auguste P, Armoiry X, et al. Clinical effectiveness and cost-effectiveness of beta-interferon and glatiramer acetate for treating multiple sclerosis: systematic review and economic evaluation. Health Technology Assessment (Winchester, England).21(52):1-352.
82. Snooks HA, Anthony R, Chatters R, et al. Support and Assessment for Fall Emergency Referrals (SAFER) 2: a cluster randomised trial and systematic review of clinical effectiveness and cost-effectiveness of new protocols for emergency ambulance paramedics to assess older people following a fall with referral to community-based care when appropriate. Health Technology Assessment (Winchester, England).21(13):1-218.

83. Soomro N, Lecouturier J, Stocken DD, et al. Surveillance versus ablation for incidentally diagnosed small renal tumours: the SURAB feasibility RCT. Health technology assessment (Winchester, England). 2017;21(81):1-68.
84. Thomas M, Bruton A, Little P, et al. A randomised controlled study of the effectiveness of breathing retraining exercises taught by a physiotherapist either by instructional DVD or in face-to-face sessions in the management of asthma in adults. Health Technology Assessment (Winchester, England).21(53):1-162.
85. Watson J, Toner P, Day E, et al. Youth social behaviour and network therapy (Y-SBNT): adaptation of a family and social network intervention for young people who misuse alcohol and drugs - a randomised controlled feasibility trial. Health Technology Assessment (Winchester, England).21(15):1-260.
86. Waugh J, Hooper R, Lamb E, et al. Spot protein-creatinine ratio and spot albumin-creatinine ratio in the assessment of pre-eclampsia: a diagnostic accuracy study with decision-analytic model-based economic evaluation and acceptability analysis. Health Technology Assessment (Winchester, England).21(61):1-90.
87. Welton NJ, McAleenan A, Thom HH, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. Health Technology Assessment (Winchester, England).21(29):1-236.
88. Williams CL, Weller S, Roberts L, et al. Timing of surgical intervention for developmental dysplasia of the hip: a randomised controlled trial (Hip 'Op). Health Technology Assessment (Winchester, England).21(63):1-84.
89. Avenell A, Robertson C, Skea Z, et al. Bariatric surgery, lifestyle interventions and orlistat for severe obesity: the REBALANCE mixed-methods systematic review and economic evaluation. Health Technol Assess. 2018;22(68):1-246.
90. House A, Bryant L, Russell AM, et al. Managing with Learning Disability and Diabetes: OK-Diabetes - a case-finding study and feasibility randomised controlled trial. Health Technology Assessment (Winchester, England).22(26):1-328.
91. Paleri V, Patterson J, Rousseau N, et al. Gastrostomy versus nasogastric tube feeding for chemoradiation patients with head and neck cancer: the TUBE pilot RCT. Health Technol Assess. 2018;22(16):1-144.
92. Peron M, Llewellyn A, Moe-Byrne T, et al. Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: systematic reviews and economic evaluation. Health Technology Assessment (Winchester, England).22(54):1-260.
93. Saramago P, Yang H, Llewellyn A, et al. High-throughput non-invasive prenatal testing for fetal rhesus D status in RhD-negative women not known to be sensitised to the RhD antigen: a systematic review and economic evaluation. Health Technology Assessment (Winchester, England).22(13):1-172.
94. Allan LM, Wheatley A, Smith A, et al. An intervention to improve outcomes of falls in dementia: the DIFRID mixed-methods feasibility study. Health Technol Assess. 2019;23(59):1-208.
95. Griffin XL, Costa ML, Phelps E, et al. Retrograde intramedullary nail fixation compared with fixed-angle plate fixation for fracture of the distal femur: the TrAFFix feasibility RCT. Health Technol Assess. 2019;23(51):1-132.

96. St James-Roberts I, Garratt R, Powell C, et al. A support package for parents of excessively crying infants: development and feasibility study. Health Technol Assess. 2019;23(56):1-144.
97. Madan I, Parsons V, Ntani G, et al. A behaviour change package to prevent hand dermatitis in nurses working in health care: the SCIN cluster RCT. Health Technol Assess. 2019;23(58):1-92.
98. Llewellyn A, Jones-Diette J, Kraft J, et al. Imaging tests for the detection of osteomyelitis: a systematic review. Health Technol Assess. 2019;23(61):1-128.
99. Drummond MF, Sculpher MJ, Claxton K, et al. Methods for the Economic Evaluation of Health Care Programmes. Oxford: Oxford: Oxford University Press; 2015.
100. Heggie R, Boyd K, Wu O. How has implementation been incorporated in health technology assessments in the United Kingdom? A systematic rapid review. Health Res Policy Syst. 2021;19(1):118.
101. Wildman J, Wildman JM. Combining Health and Outcomes Beyond Health in Complex Evaluations of Complex Interventions: Suggestions for Economic Evaluation. Value Health. 2019;22(5):511-7.
102. Marsh KD, Sculpher M, Caro JJ, et al. The Use of MCDA in HTA: Great Potential, but More Effort Needed. Value in Health. 2018;21(4):394-7.
103. Tinelli M, Ryan M, Bond C. What, who and when? Incorporating a discrete choice experiment into an economic evaluation. Health Econ Rev. 2016;6(1):31-.
104. Glassman A, Giedion U, Smith PC. What's In, What's Out: Designing Benefits for Universal Health Coverage. Glassman A, Giedion U, Smith PC, editors: Brookings Institution Press; 2017.
105. Anderson R, Hardwick R. Realism and resources: Towards more explanatory economic evaluation. Evaluation. 2016;22(3):323-41.
106. Dalkin SM, Greenhalgh J, Jones D, et al. What's in a mechanism? Development of a key concept in realist evaluation. Implementation Science. 2015;10(1):49.
107. McMeekin N, Briggs A, Wu O. PRM135 - Developing A Conceptual Modelling Framework For Economic Evaluation. Value in Health. 2017;20(9):A754-A5.
108. Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting. BMJ (Clinical research ed.). 2011;342:d1548-d.
109. Schlosser RW, Wendt O, Bhavnani S, et al. Use of information-seeking strategies for developing systematic reviews and engaging in evidence-based practice: the application of traditional and comprehensive Pearl Growing. A review. International Journal of Language & Communication Disorders. 2006;41(5):567-82.
110. Hinde S, Spackman E. Bidirectional Citation Searching to Completion: An Exploration of Literature Searching Methods. PharmacoEconomics. 2015;33(1):5-11.
111. Badampudi D, Wohlin C, Petersen K. Experiences from using snowballing and database searches in systematic literature studies. Proceedings of the 19th International Conference on Evaluation and Assessment in Software Engineering; Nanjing, China: Association for Computing Machinery; 2015. p. Article 17.
112. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ. 2005;331(7524):1064-5.

113. Claxton K, Martin S, Soares M, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. Health Technol Assess. 2015;19(14):1-503, v-vi.
114. Li J, Burnham JF, Lemley T, et al. Citation Analysis: Comparison of Web of Science®, Scopus™, SciFinder®, and Google Scholar. Journal of Electronic Resources in Medical Libraries. 2010;7(3):196-217.
115. Sculpher M. Evaluating the cost-effectiveness of interventions designed to increase the utilization of evidence-based guidelines. Family Practice. 2000;17:S26-S31.
116. Hoomans TaA, Andre and Evers, Silvia and Severens, Hans, . Worthwhile Implementation of Evidence-Based Guidelines into Clinical Practice: How to Determine the Investment Potential for Guideline Implementation and the Value for Money of Implementation Strategies? iHEA 2007 6th World Congress: Explorations in Health Economics Paper, Available at SSRN: https://ssrn.com/abstract=993206. 2006.
117. Johannesen K, Janzon M, Jernberg T, et al. Subcategorizing the Expected Value of Perfect Implementation to Identify When and Where to Invest in Implementation Initiatives. Medical Decision Making. 2020;40(3):327-38.
118. Wright SJ, Paulden M, Payne K. Implementing Interventions with Varying Marginal Cost-Effectiveness: An Application in Precision Medicine. Medical Decision Making. 2020;40(7):924-38.
119. Chamberlain CA, Martin RM, Busby J, et al. Trends in procedures for infertility and caesarean sections: was NICE disinvestment guidance implemented? NICE recommendation reminders. BMC Public Health. 2013;13(1):112.
120. Green CJ, Maxwell R, Verne J, et al. The influence of NICE guidance on the uptake of laparoscopic surgery for colorectal cancer. J Public Health (Oxf). 2009;31(4):541-5.
121. Wagg A, Duckett J, McClurg D, et al. To what extent are national guidelines for the management of urinary incontinence in women adhered? Data from a national audit. Bjog. 2011;118(13):1592-600.
122. Wathen B, Dean T. An evaluation of the impact of NICE guidance on GP prescribing. Br J Gen Pract. 2004;54(499):103-7.
123. Andronis L, Barton PM. Adjusting Estimates of the Expected Value of Information for Implementation: Theoretical Framework and Practical Application. Medical Decision Making. 2016;36(3):296-307.
124. Grimm SE, Dixon S, Stevens JW. Assessing the Expected Value of Research Studies in Reducing Uncertainty and Improving Implementation Dynamics. Medical Decision Making. 2017;37(5):523-33.
125. O'Leary MC, Lich KH, Frerichs L, et al. Extending analytic methods for economic evaluation in implementation science. Implementation Science. 2022;17(1).
126. Aarons GA, Hurlburt M, Horwitz SM. Advancing a conceptual model of evidence-based practice implementation in public service sectors. Administration and policy in mental health and mental health services research. 2011;38:4-23.
127. Saldana L, Chamberlain P, Bradford WD, et al. The cost of implementing new strategies (COINS): A method for mapping implementation resources using the stages of implementation completion. Children and Youth Services Review. 2014;39:177-82.

128. Cidav Z, Mandell D, Pyne J, et al. A pragmatic method for costing implementation strategies using time-driven activity-based costing. Implementation Science. 2020;15(1).
129. Proctor EK, Powell BJ, McMillen JC. Implementation strategies: recommendations for specifying and reporting. Implementation Science. 2013;8(1):139.
130. Vale L, Thomas R, MacLennan G, et al. Systematic review of economic evaluations and cost analyses of guideline implementation strategies. Eur J Health Econ. 2007;8(2):111-21.
131. Clarke CS, Vindrola-Padros C, Levermore C, et al. How to Cost the Implementation of Major System Change for Economic Evaluations: Case Study Using Reconfigurations of Specialist Cancer Surgery in Part of London, England. Applied health economics and health policy. 2021;19(6):797-810.
132. Hunter RM, Fulop NJ, Boaden RJ, et al. The potential role of cost-utility analysis in the decision to implement major system change in acute stroke services in metropolitan areas in England. Health Res Policy Syst. 2018;16(1):23.
133. Severens JL. Value for money of changing healthcare services? Economic evaluation of quality improvement. Quality & Safety in Health Care. 2003;12(5):366-71.
134. Gandjour A, Lauterbach KW. How much does it cost to change the behavior of health professionals? A mathematical model and an application to academic detailing. Medical Decision Making. 2005;25(3):341-7.
135. Dijkstra RF, Niessen LW, Braspenning JCC, et al. Patient-centred and professional-directed implementation strategies for diabetes guidelines: a cluster-randomized trial-based cost-effectiveness analysis. Diabetic Medicine. 2006;23(2):164-70.
136. Wright J, Bibby J, Eastham J, et al. Multifaceted implementation of stroke prevention guidelines in primary care: cluster-randomised evaluation of clinical and cost effectiveness. Quality & Safety in Health Care. 2007;16(1):51-9.
137. Hoomans T, Ament AJHA, Evers SMAA, et al. Implementing guidelines into clinical practice: what is the value? Economic evaluation of change in clinical practice. Maastricht: University Press; 2008:83–104. 2008;17.
138. Hoomans T, Severens JL, Evers SMAA, et al. Value for Money in Changing Clinical Practice: Should Decisions about Guidelines and Implementation Strategies Be Made Sequentially or Simultaneously? Medical Decision Making. 2009;29(2):207-16.
139. Hoomans T, Fenwick EAL, Palmer S, et al. Value of Information and Value of Implementation: Application of an Analytic Framework to Inform Resource Allocation Decisions in Metastatic Hormone-Refractory Prostate Cancer. Value in Health. 2009;12(2):315-24.
140. Hoomans T, Abrams KR, Ament AJHA, et al. Modeling the Value for Money of Changing Clinical Practice Change A Stochastic Application in Diabetes Care. Medical Care. 2009;47(10):1053-61.
141. Soeteman DI, Busschbach JJV, Verheul R, et al. Cost-Effective Psychotherapy for Personality Disorders in The Netherlands: The Value of Further Research and Active Implementation. Value in Health. 2011;14(2):229-39.
142. Fortney JC, Pyne JM, Burgess JF, Jr. Population-level cost-effectiveness of implementing evidence-based practices into routine care. Health Serv Res. 2014;49(6):1832-51.

143. Faria R, Walker S, Whyte S, et al. How to Invest in Getting Cost-effective Technologies into Practice? A Framework for Value of Implementation Analysis Applied to Novel Oral Anticoagulants. Medical Decision Making. 2017;37(2):148-61.
144. Mewes JC, Steuten LMG, Ijsbrandy C, et al. Value of Implementation of Strategies to Increase the Adherence of Health Professionals and Cancer Survivors to Guideline-Based Physical Exercise. Value in Health. 2017;20(10):1336-44.
145. Eisman AB, Hutton DW, Prosser LA, et al. Cost-effectiveness of the Adaptive Implementation of Effective Programs Trial (ADEPT): approaches to adopting implementation strategies. Implementation Science. 2020;15(1).
146. Heggie R, Wu O, White P, et al. Mechanical thrombectomy in patients with acute ischemic stroke: A cost-effectiveness and value of implementation analysis. International Journal of Stroke. 2020;15(8):881-98.
147. Wright SJ, Newman WG, Payne K. Quantifying the Impact of Capacity Constraints in Economic Evaluations: An Application in Precision Medicine. Medical decision making : an international journal of the Society for Medical Decision Making. 2022;42(4):538-53.
148. Walker S, Griffin S, Asaria M, et al. Striving for a Societal Perspective: A Framework for Economic Evaluations When Costs and Effects Fall on Multiple Sectors and Decision Makers. Applied health economics and health policy. 2019.
149. Gongora-Salazar P, Rocks S, Fahr P, et al. The Use of Multicriteria Decision Analysis to Support Decision Making in Healthcare: An Updated Systematic Literature Review. Value in Health. 2022.
150. Claxton KP, Sculpher MJ. Using Value of Information Analysis to Prioritise Health Research. PharmacoEconomics. 2006;24(11):1055-68.
151. Barger S, Sullivan SD, Bell-Brown A, et al. Effective stakeholder engagement: design and implementation of a clinical trial (SWOG S1415CD) to improve cancer care. BMC Medical Research Methodology. 2019;19(1):119.
152. Landes SJ, McBain SA, Curran GM. An introduction to effectiveness-implementation hybrid designs. Psychiatry Res. 2019;280:112513.
153. Scottish Intercollegiate Guideliens Network S. Management of Patients with Stoke or TIA: Assessment, Investigations, Immediate Management and Secondary Prevention. NHS Quality Improvement Scotland. 2008;Accessed on 25th April 2016. Obtained from http://www.sign.ac.uk/pdf/sign108.pdf.
154. NICE. NICE Guidance: mechanical clot retrieval for treating acute ischaemic stroke. Retrieved from https://www.nice.org.uk/guidance/ipg548. Assessed on 29th September 2016. 2016.
155. Berkhemer OA, Fransen PSS, Beumer D, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. New England Journal of Medicine. 2015;372(1):11-20.
156. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. New England Journal of Medicine.372(11):1009-18.
157. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. New England Journal of Medicine.372(11):1019-30.

158. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. New England Journal of Medicine.372(24):2285-95.
159. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. The New England journal of medicine. 2015;372(24):2296-306.
160. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. The Lancet Neurology.15(11):1138-47.
161. Wahlgren N, Moreira T, Michel P, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. International Journal of Stroke. 2015;11(1):134-47.
162. Achit H, Soudant M, Hosseini K, et al. Cost-Effectiveness of Thrombectomy in Patients With Acute Ischemic Stroke: The THRACE Randomized Controlled Trial. Stroke. 2017;48(10):2843-7.
163. Leppert MH, Campbell JD, Simpson JR, et al. Cost-Effectiveness of Intra-Arterial Treatment as an Adjunct to Intravenous Tissue-Type Plasminogen Activator for Acute Ischemic Stroke. Stroke. 2015;46(7):1870-6.
164. Authority HIaQ. HTA of Mechanical Thrombectomy for Stroke. Accessed on 29th July 2018. Obtained from https://www.hiqa.ie/reports-and-publications/health-technology-assessments/hta-mechanical-thrombectomy-stroke. 2017.
165. Ganesalingam J, Pizzo E, Morris S, et al. Cost-Utility Analysis of Mechanical Thrombectomy Using Stent Retrievers in Acute Ischemic Stroke. Stroke. 2015;46(9):2591-8.
166. Ontario HQ. Mechanical Thrombectomy in Patients With Acute Ischemic Stroke: A Health Technology Assessment. Ontario health technology assessment series. 2016;16(4):1-79.
167. 1428 MA. Mechanical Thrombectomy for Acute Ischaemic Stroke Due To large Vessel Occlusion Submission To the Medical Services Advisory Committee. 2016.
168. Kunz WG, Hunink MG, Sommer WH, et al. Cost-Effectiveness of Endovascular Stroke Therapy: A Patient Subgroup Analysis From a US Healthcare Perspective. Stroke. 2016;47(11):2797-804.
169. Arora N, Makino K, Tilden D, et al. Cost-effectiveness of mechanical thrombectomy for acute ischemic stroke: an Australian payer perspective. Journal of Medical Economics. 2018;21(8):799-809.
170. Aronsson M, Persson J, Blomstrand C, et al. Cost-effectiveness of endovascular thrombectomy in patients with acute ischemic stroke. Neurology. 2016;86(11):1053-9.
171. Ruggeri M, Basile M. Cost-effectiveness analysis of mechanical thrombectomy with stent retriever in the treatment of acute ischemic stroke in Italy. 2018:1-10.
172. Lobotesis K, Veltkamp R, Carpenter IH, et al. Cost-effectiveness of stent-retriever thrombectomy in combination with IV t-PA compared with IV t-PA alone for acute ischemic stroke in the UK. J Med Econ. 2016;19(8):785-94.
173. Steen Carlsson K, Andsberg G, Petersson J, et al. Long-term cost-effectiveness of thrombectomy for acute ischaemic stroke in real life: An analysis based on data from the Swedish Stroke Register (Riksstroke). International journal of stroke : official journal of the International Stroke Society. 2017;12(8):802-14.

174. Fiehler J, Cognard C, Gallitelli M, et al. European recommendations on organisation of interventional care in acute stroke (EROICAS). European Stroke Journal. 2016;1(3):155-70.
175. Aguiar de Sousa D, von Martial R, Abilleira S, et al. Access to and delivery of acute ischaemic stroke treatments: A survey of national scientific societies and stroke experts in 44 European countries. Eur Stroke J. 2019;4(1):13-28.
176. Allen M, Pearn K, James M, et al. Maximising access to thrombectomy services for stroke in England: A modelling study. Eur Stroke J. 2019;4(1):39-49.
177. Flynn D, Ford GA, McMeekin PJ, et al. Characteristics of intra-arterial thrombectomy service provision in England. International journal of stroke : official journal of the International Stroke Society. 2016;11(8):NP83-NP5.
178. NICE. Guide to the Methods of Technology Appraisal Accessed on 5th April 2017. Obtained from https://www.nice.org.uk/process/pmg9/chapter/the-reference-case. 2013.
179. Rivero-Arias O, Ouellet M, Gray A, et al. Mapping the Modified Rankin Scale (mRS) Measurement into the Generic EuroQol (EQ-5D) Health Outcome. Medical Decision Making. 2009;30(3):341-54.
180. Division IS. Scottish Health Service Costs Accessed on 7th November 2016. Obtained from http://www.isdscotland.org/Health-Topics/Finance/Scottish-National-Tariff/. 2016.
181. Committee JF. British National Formulary (online). London: BMJ Group and Pharmaceutical Press. Accessed on 7th November 2016. Obtained from http://www.medicinescomplete.com.
182. Glick HAD, Jalpa A & Sonnad, Seema S & Polsky, Daniel. Economic Evaluation in Clinical Trials. OUP Catalogue, Oxford University Press, number 9780198529972. 2007.
183. Davis S, Holmes,M., Simpson,E., Sutton,A. Alteplase for the Treatment of Acute Ischaemic Stroke (review of technology appraisal 122): A Single Technology Appraisal ScHARR, The University of Sheffield. 2012.
184. Dorman P, Dennis M, Sandercock P. Are the modified "simple questions" a valid and reliable measure of health related quality of life after stroke? United Kingdom Collaborators in the International Stroke Trial. Journal of neurology, neurosurgery, and psychiatry. 1997;69(4):487-93.
185. Youman P, Wilson K, Harraf F, et al. The economic burden of stroke in the United Kingdom. PharmacoEconomics. 2003;21 Suppl 1:43-50.
186. Customs HRa. HMRC exchange rates for 2016: monthly. Accessed on 15th June 2019. Obtained from https://www.gov.uk/government/publications/hmrc-exchange-rates-for-2016-monthly. 2016.
187. Unit PSSR. Unit costs of health and social care. Accessed on 15th June 2019. Obtained from https://www.pssru.ac.uk/project-pages/unit-costs/. 2016.
188. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. New England Journal of Medicine. 2018;378(1):11-21.
189. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. New England Journal of Medicine. 2018;378(8):708-18.
190. McMeekin P, White P, James MA, et al. Estimating the number of UK stroke patients eligible for endovascular thrombectomy. European Stroke Journal. 2017;2(4):319-26.

191. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation: Oup Oxford; 2006.
192. Curtis L. Unit Costs of Health and Social Care 2015. Accessed on 27th August. Obtained from http://www.pssru.ac.uk/project-pages/unit-costs/2015/. 2015.
193. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723-31.
194. Fransen PS, Berkhemer OA, Lingsma HF, et al. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. JAMA Neurol. 2016;73(2):190-6.
195. Holodinsky JK, Patel AB, Thornton J, et al. Drip and ship versus direct to endovascular thrombectomy: The impact of treatment times on transport decision-making. European Stroke Journal. 2018;3(2):126-35.
196. Wardlaw J, Brazzelli M, Miranda H, et al. An assessment of the cost-effectiveness of magnetic resonance, including diffusion-weighted imaging, in patients with transient ischaemic attack and minor stroke: a systematic review, meta-analysis and economic evaluation. Health Technol Assess. 2014;18(27):1-368, v-vi.
197. Wu O, Boyd K, Paul J, et al. Hickman catheter and implantable port devices for the delivery of chemotherapy: a phase II randomised controlled trial and economic evaluation. British Journal of Cancer. 2016;114(9):979-85.
198. Patel GS, Jain K, Kumar R, et al. Comparison of peripherally inserted central venous catheters (PICC) versus subcutaneously implanted port-chamber catheters by complication and cost for patients receiving chemotherapy for non-haematological malignancies. Supportive Care in Cancer. 2014;22(1):121-8.
199. Ryan C, Hesselgreaves H, Wu O, et al. Patient acceptability of three different central venous access devices for the delivery of systemic anticancer therapy: a qualitative study. BMJ Open. 2019;9(7):e026077.
200. Ng F, Mastoroudes H, Paul E, et al. A comparison of Hickman line- and Port-a-Cath-associated complications in patients with solid tumours undergoing chemotherapy. Clin Oncol (R Coll Radiol). 2007;19(7):551-6.
201. Taxbro K, Hammarskjöld F, Thelin B, et al. Clinical impact of peripherally inserted central catheters vs implanted port catheters in patients with cancer: an open-label, randomised, two-centre trial. Br J Anaesth. 2019;122(6):734-41.
202. Taxbro K, Hammarskjöld F, Juhlin D, et al. Cost analysis comparison between peripherally inserted central catheters and implanted chest ports in patients with cancer-A health economic evaluation of the PICCPORT trial. Acta Anaesthesiol Scand. 2020;64(3):385-93.
203. Moss JG, Wu O, Bodenham AR, et al. Central venous access devices for the delivery of systemic anticancer therapy (CAVA): a randomised controlled trial. Lancet. 2021;398(10298):403-15.
204. Wu O, McCartney E, Heggie R, et al. Venous access devices for the delivery of long-term chemotherapy: the CAVA three-arm RCT. 2021;25:47.

205. Taxbro K, Chopra V. Appropriate vascular access for patients with cancer. The Lancet. 2021;398(10298):367-8.
206. White IR. Multivariate random-effects meta-analysis. Stata Journal. 2009;9(1):40-56.
207. Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. Systematic Reviews. 2017;6(1):79.
208. Mermel LA, Allon M, Bouza E, et al. Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2009;49(1):1-45.
209. Sousa B, Furlanetto J, Hutka M, et al. Central venous access in oncology: ESMO Clinical Practice Guidelines†. Annals of Oncology. 2015;26:v152-v68.
210. McMeekin P, Flynn D, James M, et al. Updating estimates of the number of UK stroke patients eligible for endovascular thrombectomy: incorporating recent evidence to facilitate service planning. Eur Stroke J. 2021;6(4):349-56.
211. Bellos I. Multicriteria Decision-Making Methods for Optimal Treatment Selection in Network Meta-Analysis. Medical Decision Making. 2022;43(1):78-90.
212. Reeves P, Edmunds K, Searles A, et al. Economic evaluations of public health implementation-interventions: a systematic review and guideline for practice. Public Health. 2019;169:101-13.
213. Pinnock H, Barwick M, Carpenter CR, et al. Standards for Reporting Implementation Studies (StaRI) Statement. BMJ. 2017;356:i6795.
214. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ : British Medical Journal. 2013;346:f1049.
215. Krebs E, Nosyk B. Cost-Effectiveness Analysis in Implementation Science: a Research Agenda and Call for Wider Application. Curr HIV/AIDS Rep. 2021;18(3):176-85.
216. Curran GM, Bauer M, Mittman B, et al. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care. 2012;50(3):217-26.
217. Peters D, Tran N, Adam T, et al. Implementation research in health: a practical guide / edited by David Peters … [et al]. Geneva: World Health Organization; 2013 2013.
218. McMeekin N, Wu O, Germeni E, et al. How methodological frameworks are being developed: evidence from a scoping review. BMC Medical Research Methodology. 2020;20(1):173.
219. McMeekin NJM. Conceptual models in health economic evaluation: a new role. PhD thesis. Available at https://theses.gla.ac.uk/82570/1/2021McMeekinPhD.pdf. Accessed on 5th January 2023. 2021.
220. Hinde JM, Bray JW, Cowell AJ. Implementation science on the margins: How do we demonstrate the value of implementation strategies? Families, Systems, & Health. 2020;38:225-31.
221. Raghavan R. The Role of Economic Evaluation in Dissemination and Implementation Research. In: Brownson RC, Colditz GA, Proctor EK, editors. Dissemination and Implementation Research in Health: Translating Science to Practice: Oxford University Press; 2017. p. 0.

222. Knocke K, Wagner TW. The Evolving Economics of Implementation. BMJ Qual Saf. 2022;31(8):555-7.
223. Standfield L, Comans T, Scuffham P. Markov Modelling and Discrete Events Simulation in Healthcare: a Systematic Comparison. International Journal of Technology Assessment in Health Care. 2014;30(2):165-72.
224. Simpson KN, Strassburger A, Jones WJ, et al. Comparison of Markov model and discrete-event simulation techniques for HIV. PharmacoEconomics. 2009;27(2):159-65.
225. Karnon J. Alternative decision modelling techniques for the evaluation of health care technologies: Markov processes versus discrete event simulation. Health Econ. 2003;12(10):837-48.
226. Deidda M, Geue C, Kreif N, et al. A framework for conducting economic evaluations alongside natural experiments. Soc Sci Med. 2019;220:353-61.
227. Ciani O, Manyara AM, Chan A-W, et al. Surrogate endpoints in trials: a call for better reporting. Trials. 2022;23(1):991.
228. Grunwald IQ, Wagner V, Podlasek A, et al. How a thrombectomy service can reduce hospital deficit: a cost-effectiveness study. Cost Effectiveness and Resource Allocation. 2022;20(1):59.
229. Sculpher M, Drummond M, Buxton M. The iterative use of economic evaluation as part of the process of health technology assessment. J Health Serv Res Policy. 1997;2(1):26-30.
230. NIHR. Best Research for Best Health: The Next Chapter. Published: 10 June 2021. Available at https://www.nihr.ac.uk/documents/best-research-for-best-health-the-next-chapter/27778. Accessed on 1st Febriary 2023. 2023.